THE PRACTITIONER

No. 981 MARCH 1950 Volume 164

THE MONTH

The Symposium

JUDGING from the number of queries we receive on the subject, and from the persisting popularity of the symposium, diseases of the skin would appear to constitute one of the major problems of general practice. Whether this is due to their high incidence, difficulties in diagnosis, or inadequacy of modern treatment, it is difficult to say. Probably all three factors play a part. Whilst the therapeutic prospect appears brighter, there is still a hard core of conditions such as psoriasis and acne which defy the onslaught of modern advances. Because of their frequency and the difficulty they present in treatment, we have included both these conditions in this symposium. The antihistamines, like all therapeutic discoveries of the present age, have been hailed with more enthusiasm than intelligence, with the inevitable result that their undoubted value is being obscured by their indiscriminate use. It is for this reason that we have included an article on their use in dermatology. "Drug eruptions" are a perennial problem which has become accentuated by the potential dangers of sensitization to such life-saving drugs as the sulphonamides and penicillin. The recognition of the importance of "contact dermatitis" is one of the major advances in dermatological diagnosis, and a full appreciation of its significance should go far towards easing the diagnostic problems of the dermatologically minded practitioner. Last, but by no means least, is the problem of the prevention of skin lesions in industry. Much has been written about "barrier creams", but hitherto sufficient emphasis has not been placed upon the need for looking upon these useful preparations as merely part of a carefully planned scheme of prevention. The unskilled and indiscriminate use of barrier creams can do as much harm as their intelligent use can do good.

Colonial Medical Research

A LITTLE booklet with the somewhat cumbersome title of "A note on some of the scientific studies undertaken by members of the colonial medical service during the period 1930-47, with a bibliography" (His Majesty's Stationery Office, 1949, price 1s.), is both a striking tribute to the assiduity of members of the Service and a curiously ingenuous official admission of the inadequacy of the Service. "Colonial territories cannot yet afford to employ more than a fraction of the number of fully qualified medical workers who are needed . . . laboratory facilities are limited . . . few colonies are able to

provide staff and facilities for full-time research". For many years this has been a major criticism of the colonial medical service, both by members of the Service and by interested and informed outsiders, and it is to be hoped that this official confession of inadequacy will be followed by the appropriate action. One of the first steps that will need to be taken will be a correlation of the terms of service with those now pertaining in the national health service in this country. Without such correlation, and a system of interchange between the two services, it will never be possible to maintain the quality and quantity of medical men (and women) required for the colonies.

As a record of good work carried out under difficult conditions this leaflet makes impressive reading. One interesting omission is venereal diseases, and it is disturbing to be reminded of how comparatively little has been done on two of the major public health problems of the tropics—leprosy and tuberculosis. Of the 770 articles listed in the bibliography, only 9 are mentioned in the text as referring to leprosy and 14 to tuberculosis. Figures such as these can be misleading, but unfortunately these proportions are not very far from the truth so far as the practical importance attached to these two major problems is concerned. There is evidence that this outlook is changing but, as recent congresses have shown, the situation is still far from satisfactory. As in so many spheres of colonial medical work, much information must still be collected and collated in order to obtain an accurate picture of the true state of affairs, but there is no reason why investigative and curative measures should not be developed simultaneously.

A Venerable Book

To attain a centenary edition must be wellnigh a unique feature for a medical textbook. This, however, is the proud claim that Mr. John Murray can make for the recently published 40th edition of "Handbook of Physiology and Biochemistry", the revision of which since 1928 has been in the capable hands of Professor R. J. S. McDowall of King's College, London. It was in 1848 that this book was first published, the author then being William Kirkes of St. Bartholomew's Hospital. In his preface Kirkes expresses his indebtness to Mr. (later Sir) James Paget for permission to make free use of Paget's lecture notes. For practically the next fifty years successive editions were revised by a series of St. Bartholomew's men, and it was not until 1896 that the link was broken and W. D. Halliburton, then professor of physiology at King's College, took over responsibility, to be succeeded in due course by the present author. The original publishers were Taylor, Walton and Maberly of Gower Street, and it was in 1869, with the publication of the seventh edition, that the book became the property of the present publishers. In spite of the many competitors in this field that have been born during the last century, this book has kept its place as one of the students' favourites: an impressive tribute to the useful function it has subserved and to the policy of successive authors of emphasizing principles rather than details, facts rather than theories.

The Bread Problem

THE art and science of nutrition make about as uneasy bedfellows as do the art and science of medicine. The nutritional experts tell us that wholemeal bread is the solution of all our troubles, but with that perversity which has been the *bête noir* of all dictators (scientific or otherwise), the public persist in preferring a white loaf. The controversy will probably never be settled, and we have a shrewd suspicion that if free-will ever survives present political trends, the public will have their way. While this major storm rumbles on, a minor one would appear to be well on the way towards subsiding. The agene controversy came to a head with remarkable speed and, like a tropical storm, is apparently settling with equal rapidity. A scientific committee comprising representatives of the Ministries of Food and Health, the Medical Research Council and the milling industry, has recommended that agene (nitrogen trichloride) should be replaced as an "improver" of flour by chlorine dioxide. This is apparently a suitable substitute, and "extensive tests" are said to have shown that flour treated with this improver, which is used in a proportion of less than 30 parts per million, causes no toxic symptoms in man or animal. The recommendation has been accepted by both the Ministries and by the milling industry, but there will be considerable delay in making the change as necessary plant and supplies of the new improver have to be obtained from the United States. Meanwhile we are assured that the use of agene has "not been proved to be injurious in any way to human health". So ends an interesting human experiment—inconclusively as is so often the case with such experiments, and we shall probably never know whether agene has any chronic toxic effect on man. The delay in making the switch-over is unfortunate, if unavoidable, and practitioners will probably find it necessary to reassure a few of their nervous dyspeptic patients that the agenized bread they eat is not the cause of their malady.

John Radcliffe

NOT the least interesting of the "centenaries" that fall to be celebrated this year is the tercentenary of the birth of John Radcliffe, who was born at Wakefield on February 7, 1650. "A physician who owed his great success more to his natural sagacity and sound common sense than to scholarship", he proved a loyal son of Oxford, where he was educated. It is to the proceeds of the fashionable practice which he built up in London that Oxford owes the Radcliffe Infirmary, the Radcliffe Library, and the Radcliffe Observatory. It is not only as a generous benefactor that his memory persists, but also as a brilliant conversationalist in an age renowned for attainments in this particular sphere. It was Radcliffe, for instance, who was the author of the famous dictum that "as a young practitioner he possessed twenty remedies for every disease, and at the close of his career he found twenty diseases for which he had not one remedy". Although his practice was a fashionable one, and his patients included both William III and Mary, he was no respecter of persons, and William never forgave him for his remark after inspecting the

King's swollen ankles, that he "would not have His Majesty's two legs for all his three kingdoms". Characteristic of his outlook on medicine is the story that when asked where his library was, he pointed to a corner of the room where lay a herbal, a skeleton, and some bottles of drugs.

Aloes

IN these days of mass production and scientific medicine when the pharmaceutical companies of the world are vying with each other in their attempts to produce more and better drugs at cheaper prices, it is refreshing to be reminded that more leisurely methods of drug production still live on in certain parts of the world. In an interesting article in the *Pharmaceutical Journal* a correspondent describes the methods whereby aloe juice is produced in the Cape Province of South Africa. Although the plant grows freely, the amount of juice available is largely dependent upon weather conditions. A dry season, for example, reduces the amount of juice so much that the leaves, from which the juice is obtained, may only be cut in alternate years. To obtain the maximum amount of juice the leaves are cut either in the early morning or in the late afternoon. As a high wind slows the flow of juice, cutting is never carried out on windy days. Although the methods employed are essentially the same as those used 300 years ago, it is interesting to note how the "industrial hazards" of the process have been obviated. During the process of collecting the leaves the natives go on what they call a "concrete" diet, which consists of dried beans and maize. This is because they have found from experience that during the process they inevitably swallow a considerable amount of the juice, and this "concrete" diet is the one which best counteracts the irritant effect of the juice on the stomach. The irritant action of the juice on the skin is prevented by the wearing of sacking or skins on the arms. The crop is a valuable one, as the prices range from £6 10*s*. to £7 10*s*. per 100 lb. It is interesting to learn that the price obtained for the first batch exported from the Cape in 1761 was 2*s*. 3½*d*. per pound.

"To Sleep, Perchance to Dream"

LAST month the symposium on neurology contained an admirably practical article on "Disorders of sleep". It is no mere coincidence that this month's issue contains an article on "The mechanism of sleep", in which the subject is approached from a more philosophical and biological angle. The sequence is a logical one. The practitioner's main problem is the inherently practical one of how to deal with the disorders of sleep in patients. It is only in the evening when, occasionally, he can steal a moment from the insistent calls of his practice, that he can sit back in front of his own fireside and ponder over the implications of these disorders. The problem, like so many fundamental problems, is one that has resisted all attempts at solution, but we feel that Dr. Learoyd's essay will strike many sympathetic chords in the hearts of his fellow practitioners. The scientists among our readers may be sceptical, but the clinicians will appreciate this discussion of one of the fundamental mysteries of life.

PSORIASIS

By BRIAN RUSSELL, M.D., M.R.C.P.

Assistant Physician, Skin Department, St. Bartholomew's Hospital;
Physician in charge of Skin Department, Prince of Wales's Hospital;
Physician, St. John's Hospital for Diseases of the Skin.

According to Cockayne (1933) the latent inherited predisposition to psoriasis occurs as a complete and regular dominance, but it often remains dormant throughout life so that, on the average, only about one-fifth of a psoriatic's children will ever show the condition, and a little over one-eighth of the grandchildren (Romanus, 1945). Various stimuli may raise latent psoriasis to the clinical flood-tide level. These stimuli may operate any time in life, so that psoriasis may occasionally appear in the very young or the very old. The peak incidence, however, is in the second decade in females, and in the third in males (fig. 1), and the general tendency to an earlier age of onset in females is so marked that the psoriasis has developed in 42 per cent. before the twentieth birthday, in contrast to only 22 per cent. in males. An increased incidence at the menopause is not noted.

The strength of stimulus necessary to produce a psoriatic reaction varies greatly from one individual to another, so that psoriasis can be imagined as lurking at varying depths, figuratively speaking, below the clinical threshold level. Often it is only when two or more types of disturbance—infective, physical, endocrine, metabolic, emotional—happen to coincide that psoriasis results. A high family incidence implies that the inherited predisposition is only just below the threshold level, so that it may prove very difficult, or wellnigh impossible, to return the flooded river Psora to its bed, and a trivial stimulus, if it continues to operate, is enough to maintain the eruption indefinitely. On the other hand, when the family incidence is small or non-apparent, it takes a powerful stimulus to throw up the eruption, and when it is withdrawn the psoriasis may disappear entirely and never recur as the Psora returns to its normal level, well below the danger line. It follows that if the family incidence is slight or non-apparent, the psoriasis is more likely to have been set off by a severe emotional conflict or infection, and for that very reason may prove more amenable to treatment, provided it is possible to deal satisfactorily with the emotional or infective noxa. The conception of varying depths of latency is useful in deciding what treatment is necessary or is likely to succeed in any one patient.

The fundamental cause of psoriasis remains as obscure as ever. It seems most likely that it will be explained by the biochemist, perhaps as some aberration in the endocrine-autonomic mechanism. The occurrence of all gradations, from "typical" psoriasis to psoriasiform seborrhœa, lichenoid psoriasis, and even eczematoid psoriasis, suggests that slightly differing patterns of metabolic disorder may be responsible for these skin reactions.

And further, the polymorphic toxic eruptions from mepacrine or gold, for example, may show in the one patient features of the psoriatic, eczematous, lichenoid, seborrhœic and even urticarial reactions, suggesting a most complex disturbance at work, perhaps involving the liver and endocrine-autonomic system, as well as the skin.

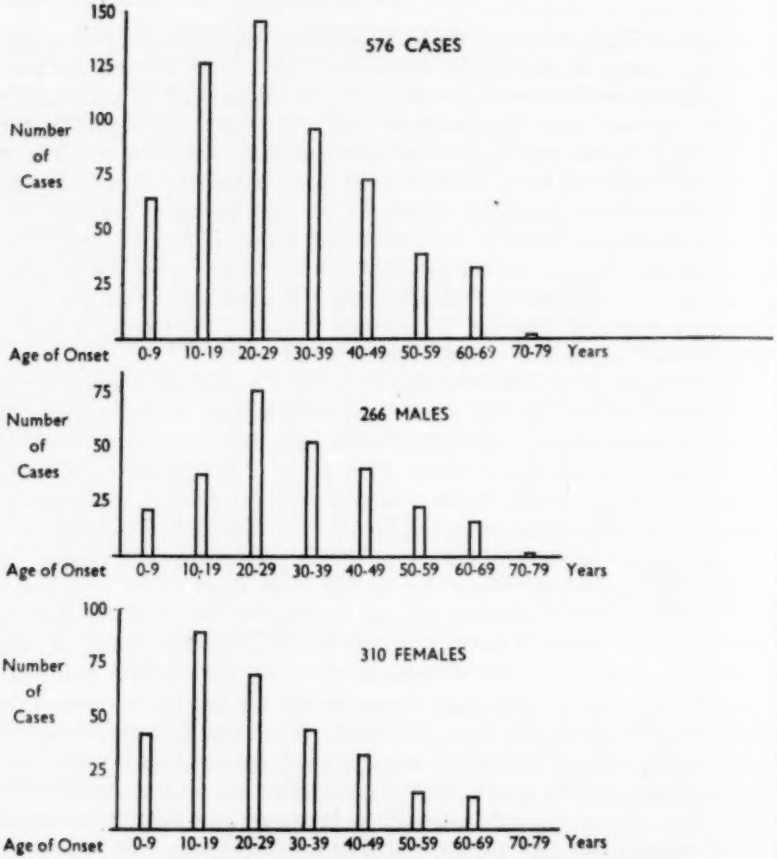


FIG. 1.—Age of onset in 576 cases of psoriasis, attending St. John's Hospital for Diseases of the Skin for the first time in 1948.

The stimuli that most commonly seem to activate or aggravate psoriasis include physical injuries to the skin, infections, and emotional upsets causing lowering of mood.

GENERAL APPROACH TO THE PSORIATIC

Psoriatics represent a cross-section of all members of the community, male and female, young and old, rich and poor. They may be otherwise apparently sound in body and mind but possess this *locus minoris resistantiæ* in the skin.

Unlike Achilles they are vulnerable all over, and the psoriatic reaction may fairly be depicted as an indication of the failure of the skin to cope properly with the physical violence, microbic assaults, and emotional stresses of life. The skin, developmentally far older than the central nervous system, is not only the physico-chemical barrier against injury, but also the sense organ for the initiation of autonomic adjustments to pleasant or unpleasant surroundings, whether they be physical or personal.

The protozoon reacts to noxious stimuli on its surface by engulfing the foe or moving away, a simple plus or minus of aggression or regression with no wavering, because hesitancy (or, as some might prefer to say, an unresolved conflict) would be fatal. With modern man, however, the situation is different, for whilst spinal reflexes provide the means of almost instantantous involuntary withdrawal from harm, the endocrine-autonomic system provides the more slowly acting mechanism of makeshift adjustment against divers continual or recurring environmental noxæ, if these cannot be disposed of voluntarily by aggression or regression. It seems that when the skin does not react effectively, psoriasis or some other skin condition results, depending upon the nature of the inborn fault. Thus the psoriatic needs protection against cold, damp, dark, and injury, the environmental darts that find the chinks in the armour. But he also needs a happy personal environment (milieu) which is as important as a favourable physical environment, although often, alas, less capable of adjustment. And lastly, if the skin condition is related to the emotional turmoil of an unresolved conflict, elevation of the spirits and the abatement of the psoriasis can only be brought about by emotional readjustment and the resultant peace of mind.

Psoriatic patients often attribute the worse phases of their skin condition to "nerves" or being "run down". Wittkower (1946) pointed out that psoriasis occurs in a diversity of personality types but that emotionally maladjusted persons are found in a much higher percentage of psoriatics than of a cross-section of the population. A specific psychological meaning for the skin disorder could not be determined, the types of maladjustment and the nature of the basic conflicts being variable. This does not imply that psoriasis is primarily a psychogenic disorder, but that in the emotionally unstable individual variations in emotional tone have a strong influence on the waxing and waning of the eruption. Emotionally stable psoriatics, on the other hand, are unfortunate in that their malady is never far below the level of activation, so that the most trivial of stimuli may set off the reaction.

The common denominator in emotionally controlled psoriasis seems to be the state of the mood, the depression of which coincides with the appearance of the psoriasis above the surface so often as to suggest a relationship analogous to the interdependent arms of a balance. In such a balance it is clear that depression may lead to psoriasis, or psoriasis to depression, the two having a mutually unfavourable influence; and further, to complete the analogy, that a third factor applying torsion at the fulcrum may cause both psoriasis and depression. Reversal of the process by the removal of dull care

from the overweighted side may, however, so tip the balance that the psoriasis is, figuratively speaking, depressed beneath the surface. There are many causes of depression, from physical illness on the one hand to unresolved superficial or deep emotional conflicts on the other. Obsessional, anxiety, hysterical, and cyclothymic states all have the common symptom of depression, and this seems the only connecting link between the different patterns of psoriatic personality. The particular event which acts as the match to the psoriatic gunpowder may be responsibility, strain, or worry that is too much for that individual, detachment from loved ones, unhappiness in the home, difficulties in adaptation to new school- or work-mates, and so on. An apparently trivial upset may have an altogether disproportionate effect if it reactivates some basic conflict.

Psoriasis in the emotionally maladjusted is of relatively good short-term prognosis because it may prove amenable to suggestion. It is well to accept that many of our empirical measures act (when they do) in this way but that relapse occurs when the "booster" to morale is discontinued.

I have recently seen a confluent and universal psoriasis gradually disappear week by week under the influence of hypnotic suggestion and soft paraffin, so that after about three months less than 10 per cent. of the surface remained involved. This was the more impressive because the patient was treated by the hypnotist as an out-patient, whereas he had previously resisted all manners of more orthodox, if empirical, treatments, with full psychiatric investigation, while an in-patient for many months. Relapse occurred within three weeks of discontinuance of the treatment.

Treatment on these lines in mentally ill patients must be regarded as symptomatic only, because it fails to remove the basic conflict responsible for the mental ill-health. Its use therefore seems limited to the production of temporary immediate improvement, and psychoanalytical methods are necessary for more permanent relief.

PLAN OF TREATMENT

The greatest disservice to a psoriatic is to give him a month's supply of ointment, with the remark that psoriasis is incurable—"You can rub this in if you like but it probably won't do any good". Relief is often difficult and removal of the fundamental cause impossible, but such discouragement can only lead to failure. The psoriatic needs moral support and personal individual attention and not some rigid, routine therapeutic formula.

The selection of treatments—physiotherapeutic, psychotherapeutic, nutritive, endocrine, and so on—depends upon the clinician's opinion of the trigger factor or factors concerned, but one thing is clear: that treatment given with enthusiasm and conviction is more likely to succeed, if only because the faith and hope so engendered in the patient raise his spirits. This seems the most reasonable explanation of the fact that a new treatment often succeeds once but not again, and that all manner of drugs, vitamins, and physio- and psycho-therapy may relieve. Amphetamine, 5 mg. every morning, is useful in depressed psoriatics, purely as a symptomatic measure to tide over a bad phase.

From the practical point of view, it is more convenient to consider different clinical types of psoriasis:—(1) chronic, local psoriasis of the extensor surface; (2) post-infective, guttate psoriasis; (3) exacerbation and dissemination of localized psoriasis, including psoriasis universale; (4) psoriasis, usually severe and widespread, with polyarthritis; (5) psoriasis of the scalp; (6) flexural psoriasis; (7) pustular psoriasis of the palms and soles; (8) psoriasis of the nails.

CHRONIC LOCALIZED PSORIASIS

Longstanding, chronic, localized forms arise in emotionally stable and otherwise healthy individuals and call for no active measures apart from the avoidance of local trauma and the use of a bland application, such as soft paraffin, simple ointment (B.P.), or ointment of wool alcohols. In fact, excessive zeal in treatment may have the opposite effect to that desired, by awakening the sleeping dog that would better be left to lie. This type of psoriasis may even arise from contact with plaster of Paris splints or zinc and gelatin bandages applied to the skin of a latent psoriatic who is just below the threshold level. If treatment is considered essential, thorium-X, 1000 to 2000 electrostatic units in 1 ml. of spirit, applied at fortnightly intervals for up to six treatments, is a safe and useful remedy.

POST-INFECTIVE GUTTATE PSORIASIS

Post-infective guttate psoriasis, developing ten to thirty days after infections, has also been called "streptococcal psoriasis", but as it may occur after almost any febrile state, it seems more likely that the psoriatic exanthem represents a disturbance specific to the host but nonspecific as regards the type of infecting organism, although streptococci are probably the most common cause. The disturbance of metabolism caused by the fever seems to act as the trigger mechanism, but post-infective depression may also have some influence. The patient with this type of psoriasis should be treated by rest in bed, and the application of a bland cream, as for example, calamine liniment. More active measures, such as mercurial ointments or "dithranol", should not be used because of the risk of gross aggravation and even exfoliative dermatitis from their use.

EXTENSIVE DISSEMINATED PSORIASIS

Exacerbations and dissemination of localized psoriasis represent skin reactions to various general or focal infections or physical and psychological injuries. Drug intoxication also may sometimes be responsible, but psoriasis does not represent a skin reaction to surface chemical insult which produces, even in the psoriatic, the characteristic eczematous reaction. Psoriasis may be stirred into an exfoliative reaction by over-treatment, and there is some evidence to suggest that this condition, which can also arise from arsenic or gold, indicates liver damage from absorption of hepato-toxic chemicals, applied over a large area of the skin surface. The patient with widespread psoriasis responds far better if investigated and treated in

hospital. This provides the necessary rest in bed, temporary detachment from personal cares and detrimental environmental conditions, and relief from responsibilities; it also gives a sense of hope, comfort and well-being from the active care and attention that are received.

A careful search must be made for foci of infection, the effective surgical or drug elimination of which may lead to partial or complete relief of the present psoriatic episode. Tuberculosis and syphilis must not be forgotten. An active tuberculous focus may aggravate psoriasis and a psoriasiform syphilide may represent the type reaction of the latent psoriatic to the spirochæte. It is important to relieve itching, if present, because scratch injury to the skin may aggravate psoriasis and produce new lesions (Kæbner's phenomenon). In subacute cases, hydrous ointment is useful, and an ointment such as a 6.25 per cent. solution of coal tar in ointment of wool alcohols usually gives relief in more chronic cases. The application by the practitioner in person of some remedy is often advantageous, and for this purpose "tar dermament", a 6 per cent. crude coal tar preparation in resinous base, is both clean and useful. Internal sedation may be given with sodium amytal, 1 to 3 grains (0.065 to 0.2 g.), thrice daily, and butobarbitone, 3 grains (0.2 g.), in the evening.

Excellent results may be obtained with *the Gœckerman regime*, which may be regarded as a combination of physio- and psycho-therapy, consisting, in essence, of an active treatment throughout the day, combining the soothing effects of warm baths with the stimulating and light-sensitizing action of tar applications, and the beneficial effects of ultra-violet irradiation. Autohæmotherapy is also carried out, the details of the regime being as follows:—

Two to four per cent. of crude coal tar in zinc paste is well rubbed into the lesions by hand. Next morning this paste is removed with liquid paraffin, leaving a thin film of oil and tar on the skin. Ultra-violet ray treatment is then given, the body surface being divided into six areas, one of which is treated each time, so that the whole surface is treated in six days. To these areas a first degree erythema exposure is given. The psoriatic patches receive a second degree exposure. After the light treatment, the patient takes a plain soap and water, or an oatmeal, bath, and soaks for one-half to two hours, removing the scales that will rub off (a bath of "liquor carbonis detergens" may be given instead of the oatmeal bath for thick, resistant lesions, careful watch being kept for any aggravation). After drying, a thick coat of tar paste is again applied to the lesions. Autohæmotherapy, 10 millilitres twice a week, is also given. This regime is continued for two to four weeks. Ellis (1948) has described a modification suitable for out-patients, using "liquor carbonis detergens" three times a week. He noticed, however, no significant difference whether or not ultra-violet irradiation was used in addition.

The use of dithranol for psoriasis is best reserved for in-patients. It is not a safe remedy for uncontrolled use in the home, but fortunately dithranol ointment (B.P.) is too weak to be dangerous. For in-patients, dithranol may be applied in a strength of ½ per cent. in soft paraffin (strong dithranol ointment, N.F. 1949, contains 1 per cent.), and the percentage of dithranol may be increased up to a maximum of 2 per cent. (It is important to remember that paraffin has a mitigating influence on dithranol and that, if this substance is prescribed in ointment of wool alcohols, toxic symptoms may arise from

absorption, or exfoliative dermatitis may result.) Its use should be continued until the treated areas are paler than the surrounding skin, and it should not be used in very extensive eruptions, or about the head and neck, or on the hands, because by contact it may cause an acute conjunctivitis, and it will stain the hair and bedding. The use of dithranol should be confined to chronic, resistant cases, being a symptomatic alleviation of the end-results rather than an attempt to deal with the cause.

PSORIASIS AND POLYARTHRITIS

The common association of polyarthritis with a severe form of psoriasis seems established beyond doubt. Wassmann (1949) found psoriasis seven times as common with polyarthritis (31 in 1000 patients) as with general medical disorders (43 in 10,000 patients). Both disorders fall into the category of non-specific diseases with a familial predisposition and precipitation by environmental causes (climate, work, leisure, housing, close human contacts), infections (acute and chronic, specific and non-specific, focal and general), emotional strains, faulty nutrition and metabolic disturbances. Both disorders tend to get better in pregnancy and with jaundice, and recent studies of treatment with cortisone support the conception of rheumatoid arthritis as a breakdown of adaptation in the endocrine-autonomic system to non-specific stresses. The occurrence of psoriasis from similar strains suggests that a comparable process is at work but that the inherited latent psoriatic disposition is necessary for the simultaneous development of the two disorders. A severe psoriasis is usual in these cases, indicating that the stress must be bad or the predisposition marked if this combination is to result, whereas milder strains may act first only on one organ of inherited inferiority, causing either rheumatoid arthritis or psoriasis. The similarity goes further, because the types of emotional upset depicted by Dunbar (1943) as related to rheumatoid arthritis (difficulties of environmental and sexual adjustment, distaste for responsibility, and desire for protection) are very similar to those operating in maladjusted psoriatics. The life situation before the onset, disruption of emotional attachments through change of environment, separation of parents, hardships, and so on, are similar in the two conditions. The early reports of treatment with synthetic cortisone or A.C.T.H. of arthropathic psoriasis seem no more spectacular than those often obtained by many other treatments. Hench (1949) has reported relief. Spies (1950) has described improvement within three days of beginning treatment, but no complete clearance. It is interesting to note that the patient also experienced a remarkable psychological elation. The skin condition began to relapse about a week after treatment was stopped. Other treatment is on the lines for non-specific diseases: physiotherapeutic and psychotherapeutic, by warm baths, radiant heat, infra-red rays, wax baths, diathermy, general ultra-violet rays, autohæmotherapy, T.A.B., and every possible means of instilling encouragement and hope, so as to enable the patient to cope adequately with life's problems.

PSORIASIS IN SPECIFIC AREAS

Psoriasis of the scalp may cause pruritus or it may itself arise from scratching an itchy head. Injury from combs and brushes may also play some part. This condition therefore, like all other forms of psoriasis, may have somatic or psychological significance. The best local applications for its control include the following:—In mild cases, "pragmatar" ointment is useful. More resistant cases may require 2 per cent. of ammoniated mercury, with 12½ per cent. of solution of coal tar in emulsifying ointment, to which may be added 2 to 5 per cent. of salicylic acid. Oil of cade, 12½ per cent., may be substituted for the solution of coal tar, sometimes with better effect.

Psoriasis of the flexures is an unusual form, usually associated with severe pruritus. It may represent Kœbner's isomorphic reaction to scratch injury on a large scale. Its control depends upon the discovery and the treatment of the cause of the pruritus, which may be physical (diabetes, threadworms, vaginal discharges) or, more often, psychogenic. Local applications that may help include magenta paint (B.P.C.), to the psoriasis itself, and 2 per cent. silver nitrate in nitrous spirits of ether, to any associated fissures. Obstinate patches may respond well to the local application of thorium-X, 1,500 electrostatic units per millilitre, at intervals of two weeks, for three to six treatments, but this remedy may occasionally aggravate in moist areas.

Pustular psoriasis of the palms and soles differs in no way from other forms as regards its etiology but is more intractable. Local injuries and infections, particularly hæmolytic streptococcal tonsillar infections, may be responsible. A psychological basis also seems well established in some cases:—

A patient developed this condition after the death of her husband which suddenly threw upon her the responsibility of running his catering business. The discovery that she was being deceived and cheated by her late husband's partners made her lose her trust in men, and her skin reaction seemed to symbolize her inability to stand on her own.

Psoriasis of the nails, also, is most resistant to treatment. Inquiry must be made into possible local injury from work or from habits such as nail picking. Often no cause is apparent. The condition may improve with the local application once a fortnight of thorium-X, 1,500 electrostatic units per millilitre, or from fractional X-ray irradiation. Solution of arsenic, 3 to 6 minims (0.2 to 0.35 ml.), three times a day, may also be given a trial in this intractable form of psoriasis, but its use should be limited to six weeks. The possibility must always be borne in mind when using this drug that ten or twenty years later undesirable results may follow, such as keratosis and carcinoma of the skin.

References

Cockayne, E. A. (1933): "Inherited Abnormalities of the Skin and its Appendages", London, p. 361.
Dunbar, F. (1943): "Psychosomatic Diagnosis", New York.
Ellis, C. C., *et al.* (1948): *J. invest. Derm.*, **10**, 455.
Hench, P. S., *et al.* (1949): *Proc. Mayo Clin.*, **24**, 181.
Romanus, T. (1945): *Acta Derm. Venerol.*, **26**, Supplement XII.
Spies, T. D. (1950): *Lancet*, **ii**, 11.
Wassmann, K. (1949): *Ann. rheum. Dis.*, **8**, 70.
Wittkower, E. (1946): *Lancet*, **i**, 566.

THE PROBLEM OF ACNE

By BERNARD C. TATE, M.D., F.R.C.P.

Physician, Skin Departments, United Birmingham Hospitals; Clinical Lecturer in Dermatology, University of Birmingham.

THE term "acne" has been applied to several different eruptions which have little in common save a superficial morphological similarity. Most of these eruptions are important because their presence connotes constitutional disease, but chief place must be given to acne vulgaris because of its great frequency: probably no adolescent escapes it entirely. It rarely gives rise to pain or irritation, and never endangers life, but the disfigurement of its active phases and of the permanent scarring which sometimes results from it does cause much mental suffering. It is this disease which I propose to discuss.

CLINICAL FEATURES

Acne vulgaris is so well known that it can hardly be mistaken for anything else, but other diseases, especially rosacea and facial tuberculides, are sometimes mistaken for acne, so that a brief recapitulation of its salient features may not be out of place. Acne is always accompanied by seborrhœa oleosa, although the converse is not true; a skin with large sebaceous glands freely exuding their secretion may be free of acne. The eruption is polymorphous. The primary and essential lesion is the comedo, and without comedones the diagnosis of acne vulgaris is inadmissible. Comedones may be the only lesions present, constituting acne punctata or, more familiarly, "blackheads". Usually, around some of the comedones red inflammatory papules form (acne papulosa), and in more severe cases many of the papules suppurate (acne pustulosa). The pustules may discharge, or dry up, forming crusts which drop off and leave small superficial scars, often pigmented for a time. Sometimes the inflammatory process involves the whole of the pilosebaceous follicle, and may extend into the subcutaneous tissue forming hard, indolent, and sometimes painful nodules, which may be gradually absorbed or may form abscesses which sometimes track under the skin, occasionally producing a network of cavities (acne indurata). Cyst formation, resulting from blocking of follicles by comedones, occurs not infrequently, especially on the back and sides of the neck and behind the ears in young men. In addition, superficial staphylococcal pustules are common in follicles without comedones, but these are not in any way peculiar to acne.

Acne indurata always leaves scars, but scarring may occur also in cases in which comedones preponderate from atrophy of follicles due to long-continued obstruction, and also from damage to the follicles caused by injudicious squeezing.

Acne picks out those regions where the sebaceous glands are largest; the face, especially the forehead, temples, cheeks, chin and sides of the nose;

sternal region; shoulders and interscapular region, and sometimes the whole of the back, but it never extends below the waist. The areas of predilection are often affected unequally; the face may show a severe eruption, whilst the trunk is clear, or *vice versa*.

PATHOLOGY

The cŏmedo, when extruded by pressure, looks like a small worm with a black head. The fore-part consists of a mass of concentrically arranged layers of horn cells enclosing considerable numbers of *Corynebacterium acnes* and a variable quantity of sebum, the blackness of the tip being due to oxidation of keratin. The "tail" consists of semi-solid sebum and also contains *C. acnes* and sometimes the minute acarus *Demodex folliculorum*. The horny mass forms a plug in the follicle above the opening of the sebaceous gland.

The superficial pustules not related to comedones show the ordinary changes of inflammation; but the true acne pustules, and especially the deep indurated nodules and abscesses, may be surrounded by a dense granulomatous mass containing plasma cells, multinucleated cells and fibroblasts. The nodules contain only *C. acnes*, but staphylococci may often be found in addition in the true acne pustule.

ETIOLOGY

An association between acne vulgaris and adolescence is common knowledge, and a close correlation between the onset of puberty and the formation of comedones was clearly demonstrated by Bloch (1931). At puberty there is a great increase in the production of both androgens and œstrogens by both sexes, but there seems to be no doubt that it is the androgens which determine the formation of the comedones. Eunuchs do not suffer from acne, but the eruption may be provoked in eunuchs, post-pubertal castrates and eunuchoids, as well as in women and girls, by the administration of androgens, and withdrawal of the hormone in these cases is followed by disappearance of the eruption. As Bloch pointed out, males tend to be more severely afflicted with acne than females. Acne is always accompanied with seborrhœa oleosa, and it can be shown experimentally that administration of androgens causes proliferation and increased activity of the sebaceous glands, whereas œstrogens produce the reverse changes. Finally, administration of œstrogens in sufficient quantity will cure acne in both sexes.

The mode of action of androgen in the production of comedones is not clear. The constant presence of the *C. acnes* in the comedones and pustules at once suggests that this bacillus is the cause of the eruption, but it is a normal inhabitant of the skin. It could be argued that its growth is so favoured by the increased sebaceous secretion evoked by androgens that it becomes pathogenic; but it is found in very large numbers on many skins completely free from acne. Barber (1948) postulates that comedo formation is part of a general stimulation to keratinization exerted by androgen. But why are comedones formed only in certain follicles with large sebaceous

glands? All the follicles on the face, trunk and limbs will produce comedones if stimulated to do so by chlorine, tar or mineral oils, as well as by some vegetable oils and animal fats, if rancid. It seems probable therefore that it is the sebum itself, which, produced in large quantities under the influence of androgen, and perhaps differing chemically from the sebum of childhood and of maturity, stimulates keratinization of the mouths of the follicles. This, however, remains a matter of speculation until more precise information on the chemistry of sebum is available. The formation of pustules and nodules may be due to the activity of *C. acnes* and perhaps staphylococci pent up in the blocked follicle, but the changes observed could equally be a tissue reaction to the presence of an abnormal chemical substance.

This hypothesis of the pathogenesis of acne vulgaris presents several difficulties. The disease should be most severe in the most virile youths, but the majority of males affected are of the "weedy" type. In those over eighteen I have observed that a feminine distribution of pubic hair is more common than a typical masculine distribution. The more virile youth, of course, usually indulges in vigorous outdoor sport, the therapeutic affect of which may outweigh the action of androgen. Aggravation of the disease would be expected to follow administration of androgen to males, but often the reverse is the case, especially in the weedy type, and I have found it a valuable form of treatment, not only improving the skin, but also resulting in a general increase of physical and mental vigour. The spontaneous cure which so often occurs in early adult life is difficult to explain. Increased œstrogen formation could account for it in women but not in men. Acne in men can usually be cured with œstrogen only if given in amounts which cause enlargement of the breasts, diminished physical energy and loss of libido; the very opposite state of a healthy young man. Lastly, acne does occur sometimes in infants of both sexes in whom there is no demonstrable endocrine abnormality.

Greater knowledge of the chemistry of androgens, and there may be some as yet undiscovered, and improved methods of hormone assay may resolve these difficulties. Further study of the chemistry of sebum is also desirable. Rothman (1945) has shown that hair undergoes chemical changes at puberty and that the spontaneous cure of ringworm which occurs then is due to an increase of a particular fatty acid. Analogous changes may take place in sebum, its final adult composition perhaps being gradually established over a number of years.

The androgens responsible for comedo formation are, presumably, derived from the adrenal glands in females, and from the adrenals and testes in males. These glands, however, act in concert with the other endocrine glands and it is therefore natural to look for other endocrine influences in acne, but Lipman Cohen (1941), in an extensive review of the subject, was unable to find any definite evidence of endocrine influence apart from the sex hormones.

CAUSAL FACTORS

Alimentary factors.—Both the quantity and composition of the sebum can be altered by diet. Secretion is increased in amount by a high carbohydrate diet; and the sebaceous glands, besides elaborating a secretion of their own, may take up fats directly from the blood, so that the kinds of fat eaten may affect the composition of the sebum. Further, susceptibility to cutaneous infection is increased by water retention in the skin, and this is promoted by a high carbohydrate and fat diet, as well as by ingestion of excessive quantities of salt and fluids. A high protein intake, on the other hand, promotes diuresis through the action of urea and xanthines derived from protein and nucleoprotein, and thus decreases "hydration" of the skin (Földes, 1933). Adolescents are notorious for their liking for chocolate, pastry, rich cakes and "chips"; and at the same time their output of physical energy is often lessened as a result of entry into office or factory or study for examinations, so that, if they indulge their fancies, their protein intake is likely to be diminished. Clinical experience admits of no doubt that these foods aggravate acne, and I believe that the foregoing explanation of their deleterious action is the correct one. A premenstrual increase of the superficial pustules, a common feature of acne in girls, is probably due to water retention rather than to direct action of the sex hormones on the skin.

Whitfield (1934), whose views must always command respect, regarded dyspepsia as one of the most important causative factors. Although, in a wide sense of the term, this is common, I think it is merely a concomitant symptom caused by over-indulgence in carbohydrate and fatty foods, and insufficient exercise. Several observers have sought to incriminate food allergy, but I have never found any evidence of this.

Psychological factors.—Wittkower (1948) describes typical acne patients as diffident on examination, quiet and well mannered. Their upbringing has usually been puritanical and their puberty "stormy". Serious and hard working, often deeply religious, disdainful of frivolity, they are rigid, dogmatic and intolerant in their views. They are emotionally stunted or retarded. Although apparently meek, they harbour aggressive phantasies and impulses. Shy and self-conscious in general, they are ill at ease in the presence of members of the opposite sex. Masturbation is rarely practised: "Emphasis on their moral restraint indicates a struggle within themselves between a desire for sexual expression and prohibiting forces, resulting in severe feelings of guilt". Since reading Wittkower's article, I have recognized this type more frequently, but by no means all acne patients conform to it. According to popular belief, in some quarters at any rate, the sufferer from chronic acne is a habitual masturbator. Several patients who have confessed to the habit without being asked, have also volunteered the statement that fresh pimples always appear after masturbation.

Inborn susceptibility.—As in many other diseases, this plays a big part in determining the severity of acne. Seborrhœa oleosa, the prerequisite of acne,

is to some extent a racial character, and often runs in families. Individual susceptibility is particularly well illustrated by the response of post-pubertal male castrates to the action of androgen: this produces the worst eruptions in those who have been most severely affected in adolescence.

TREATMENT

Since acne vulgaris is primarily a manifestation of endocrine activity, it is natural to turn first to hormones in treatment. Many patients can, however, be cured by other methods, and as there are certain hypothetical risks attendant on hormone therapy, it seems wiser to reserve this for the more severe and resistant cases.

Diet.—From theoretical considerations it seems that carbohydrates, fat, and salt should be restricted, the amount of fluid carefully regulated, and discrimination should be exercised on choice of fats. It is difficult at present to put these principles into practice because the quantity of protein which should be given is compulsorily restricted. It is possible, however, for patients to abstain from certain foods, the adverse effects of which are known from clinical experience as well as from theoretical considerations. The following must be rigidly excluded:—Pastry, suet puddings, fancy cakes, sweet biscuits, chocolate, cocoa, white bread, porridge, fried foods.

The quantity of salt in food depends largely upon the cook, but patients should be advised not to add salt, and highly salted foods such as kippers and anchovies should be forbidden. Many patients have the impression that the so-called "acid fruits" are harmful: rhubarb, gooseberries, strawberries, raspberries, and stone fruit, as well as fruit "squashes". This may well be so on account of the large amount of sugar which is usually added to make them palatable.

Cheese has a bad reputation in acne vulgaris, and I used to forbid it altogether, but I do not think this justifiable in present circumstances, for cheese has a high protein content besides being rich in fat. Coffee seems to me to be harmful, although I do not know of any theoretical reason why it should be. Choice of fats is important, but again this is limited by circumstances outside the patients' control. Fats with a high melting point, such as suet and that contained in chocolate, should be avoided if possible.

Lean meat, liver, kidneys, sweetbread and poultry are allowed in any quantity that can be procured. Fish is a valuable source of protein, but unfortunately most palates soon weary of it, even the forbidden fried fish. Grilled bacon and ham are not harmful in the amounts available. Eggs are popularly supposed to be bad for many skin complaints, including acne and boils. Clinical experience has convinced me that there is something in this belief, but I think it is safe to allow up to one daily. Cooked vegetables of all kinds, salads and raw fruit form an essential part of Földes's anti-retentional diet. I advise about a pound of raw fruit daily, choice being left to the patients, most of whom cooperate willingly in this, but many jib at

the vegetables. Nuts contain a good deal of protein, and I do not consider that the quantity or kind of oil in them is harmful.

Milk puddings are allowed: very few adolescents seem tempted to over-indulge in them. Cooked fruits are restricted in so far as a large quantity of sugar is often necessary to overcome their sour taste. In general the desire for sweets and puddings is much diminished if sufficient raw fruit is eaten. No fixed quantity of bread, butter and preserves can be laid down. If wholemeal bread only is eaten, and none allowed at the main meals of meat and vegetables, over-indulgence is unlikely.

The total quantity of fluid, apart from that contained in food, should be roughly three pints daily, and this may include up to one pint of milk, in spite of its relatively high fat content.

The diet must, of course, be adapted to each individual case. Active youths indulging in vigorous physical exercise or engaged in heavy manual work obviously need much more carbohydrate and fat than those in sedentary employment.

Drugs.—There is no drug which has a specific or dramatic effect on acne. The old-fashioned calcium sulphide (B.P.C.), given as a pill, 2 grains (0.13 g.) thrice daily, is sometimes beneficial. White mixture (B.P.C.), another traditional remedy, also seems to help some cases, especially if there is much pustulation, possibly because of its dehydrating action. Whitfield believed that products of bacterial putrefaction, absorbed from the intestine, alter the composition of the sebum and aggravate the disease, and claimed considerable success from the use of intestinal antiseptics. Salts of tin and of manganese have their advocates, but I have not had any success with them. In my experience, sulphonamides and penicillin have no place in the treatment of acne.

Vaccines are probably valueless in acne, except perhaps in treatment of the not infrequent concomitant staphylococcal pustules.

LOCAL THERAPY

Many mild cases can be cured by local treatment alone. The most generally useful drugs are sulphur, resorcin, and perchloride of mercury. These may be lethal to *C. acnes* and staphylococci, but their main action is to cause slight peeling of the skin, shelling out the comedones from the ostia of the follicles. Application of a greasy base seems like adding insult to injury, but this is not so, and when comedones preponderate, a paste or emulsion often seems better than a lotion. Everyone has favourite applications; mine are:—

(1) For the average case:—

Precipitated sulphur	90	grains (6 g.)
Calamine powder	120	grains (8 g.)
Zinc oxide powder	120	grains (8 g.)
Glycerin	90	minims (5.5 ml.)
Industrial methylated spirit	1½	ounces (43 ml.)
Camphor water	to 8	ounces (230 ml.)

This is gently rubbed in and allowed to dry, each night, after the skin has been thoroughly washed and dried. In fair-skinned subjects, especially if red haired, it is well to start with less sulphur, e.g. 30 grains (2 g.); whilst in dark, thick skin sulphur may have to be considerably increased.

(2) For acne punctata I use a paste as recommended by Goldsmith (1936):—

Precipitated sulphur	30 grains (2 g.)
Resorcin	30 grains (2 g.)
Zinc oxide powder	90 grains (6 g.)
Powdered starch	90 grains (6 g.)
Soft paraffin	to 1 ounce (28.5 ml.)

This also is applied each night, after preliminary washing, until slight exfoliation occurs. If necessary, the sulphur and resorcin may be gradually increased at the expense of the starch and zinc oxide. Some patients find they can control exfoliation best by a combination of the two: paste once or twice a week, and lotion the rest of the time.

Emptying of the follicles by pressure is a useful adjuvant if performed skilfully, but it is very easy to damage the follicles and produce scarring. *Ultra-violet rays* will also produce exfoliation, and in many cases a temporary clinical cure of acne. They do, however, stimulate keratinization, so that when the exfoliative effect has passed off, the condition may be worse than ever. Ultra-violet rays should therefore be followed by other treatment.

X-ray therapy is also effective in acne, probably acting by inhibiting keratinization and sebaceous secretion. It carries a potential risk of causing atrophy and telangiectasia, but I have never known this to occur when treatment has been given by a competent radiotherapist. X-rays may be used after a course of ultra-violet rays, but the reverse procedure should never be adopted. Exposure to ultra-violet rays immediately or soon after X-rays, greatly increases the risk of telangiectasia.

HORMONE THERAPY

Since androgens initiate the primary changes in acne vulgaris, œstrogens might reasonably be expected to have a curative effect, and indeed, it is possible to cure acne in both sexes with œstrogens. In *the female* one might attempt to stimulate œstrogen formation by giving gonadotrophic hormone, or œstrogens themselves could be administered. I have had no success with the first method, but many cures with the second. It seems immaterial which œstrogen is used, but oral administration is much more convenient than injection. I have used chiefly stilbœstrol, hexœstrol and ethinyl œstradiol. There is no fixed dosage, but usually only relatively small amounts are required. With ethinyl œstradiol, for instance, I start with 0.01 mg. daily, and in many cases no increase is necessary. Whether or not it is desirable to alter the dose according to the phase of the menstrual cycle seems doubtful. Natural œstrogens are produced both before and after ovulation, although

not in the same quantities, but no harm seems to result from continuous administration of a small dose of œstrogen. Risk is negligible, but it must be remembered that "the administration of any hormone will inhibit the secretion of the corresponding hormone of the pituitary gland which normally gives rise to its production" (Simpson, 1948); and there is some evidence that œstrogens are carcinogenic. In the dosage used for acne, these risks seem so remote that one should not hesitate to employ œstrogens in severe cases in which scarring is likely, or in cases resistant to other therapy.

In *the male*, œstrogens, to be effective, must be given in such large doses that unpleasant symptoms ensue. Spermatogenesis is inhibited, and opinion is not unanimous concerning the permanency or otherwise of some of the changes observed. I consider that œstrogen therapy in the male is rarely, if ever, justified. Androgen therapy would be expected to aggravate the disease, as it sometimes does, but often the reverse is true. This may be due to a general stimulation of metabolism rather than to specific action of androgen on the skin. It is well worth trying in the weedy asthenic type if other measures fail. Again dosage has to be suited to the individual case: usually I start with methyl testosterone, 25 mg. daily. If the condition deteriorates, on this dose, an increase sometimes, paradoxically, brings about improvement.

Other endocrine preparations have been advocated by various observers, especially thyroid, but I have not had obvious success with any.

SUMMARY

Acne still remains a problem. Although it can be stated that androgens initiate the primary change, their mode of action is unknown, and the spontaneous cure, common in early adult life, is unexplained. The course of the disease is influenced by many intrinsic and extrinsic factors, among which diet is perhaps the most important. Treatment of acne, based on the theoretical considerations outlined, as well as on clinical experience, is discussed briefly.

References

Barber, H. W. (1948): "Modern Trends in Dermatology", (R. M. B. MacKenna), London, p. 125.
Bloch, B. (1931): *Brit. J. Derm. Syph.*, **43**, 61.
Cohen, E. L. (1941): *Ibid.*, **53**, 231, 269.
Földes, E. (1933): "A New Approach to Dietetic Therapy", Boston.
Goldsmith, W. N. (1936): "Recent Advances in Dermatology", London, p. 476.
Rothman, S. (1945): *Proc. Soc. exp. Biol., N.Y.*, **60**, 394.
Simpson, S. L. (1948): "Major Endocrine Disorders", London, p. 359.
Whitfield, A. (1934): *Brit. J. Derm. Syph.*, **46**, 257.
Wittkower, E. (1948): "Modern Trends in Dermatology" (R. M. B. MacKenna), London, p. 245.

DRUG ERUPTIONS

By J. KINNEAR, O.B.E., M.D., M.R.C.P.Ed.

Physician for Diseases of the Skin, Dundee Royal Infirmary; Lecturer in Diseases of the Skin, University of St. Andrews.

Eruptions due to the ingestion or injection of drugs have always been of interest and importance, but with the introduction of chemotherapeutic and antibiotic remedies their frequency and importance have increased considerably: in addition to their greater therapeutic activity these drugs show a greater tendency to produce unwanted side-effects, including skin manifestations, sometimes of serious significance.

CAUSAL FACTORS

Hypersensitivity, innate or acquired, may be said to be the cause of most drug eruptions, but in many cases the method of production is still uncertain, and in these cases the designation has merely been changed from the old-fashioned "idiosyncrasy". On the other hand, especially with the antibiotics, the phenomena may follow the pattern of a true allergic reaction. Local sensitization of patches of skin is found in the so-called fixed drug eruptions in which every time a drug is administered the same type of eruption appears on the same areas of skin. In a few cases sensitization seems to play no part, and a drug will produce the same reaction in all subjects. This is found in the yellow staining of the skin and conjunctiva after mepacrine administration, or the keratosis produced by the long-continued taking of arsenic. An eruption may be due not to the direct effect of the drug on the skin but to its action on some other system of the body which in turn affects the skin. This is seen in the purpura or other hæmorrhagic eruption which follows the administration of dicoumarol if it is allowed to produce excessive lowering of the prothrombin level in the blood. In some cases a drug exerts a trigger action and lights up a dormant infection: for example, herpes zoster may occur during the administration of arsenic and an attempt may be made deliberately to bring a latent syphilis to light by a provocative dose of an antisyphilitic drug. There are very few drugs which have not at some time or other been accused of producing an eruption; the saline laxatives and cascara are notable examples of this small group.

DIAGNOSIS

Some drug eruptions, by their appearance or distribution, give to the practised eye the clue to their cause, but in many cases the eruption itself is non-specific: an erythema, an urticaria or a rash resembling one of the eruptive fevers. If it is known that a drug apt to produce an eruption is being administered, such as one of the heavy metals, a sulphonamide or one of the

antibiotics, the diagnosis may be easy, but especially if the drug is self-administered, as in the case of laxatives or analgesics, it may not be so simple. Phenolphthalein is a common ingredient of proprietary laxatives and is a not uncommon cause of a fixed drug eruption. The quantity of such preparations swallowed by the community must be enormous; during 1946, Sweden consumed half a ton of phenolphthalein. A drug eruption should be suspected when a more or less generalized eruption appears suddenly, possibly resembling one of the eruptive fevers, if these and gastro-intestinal (including parasitic) causes can be eliminated. The fixed drug eruptions should also be remembered: fixed erythematous patches, often unusually tinted, possibly of long duration when the drug, perhaps a laxative, has been taken over a long period. A very careful inquiry should be made as to any drugs being taken, especially laxatives containing phenolphthalein, or analgesics such as aspirin, or sedatives such as phenobarbitone. The use of iodized table salt is not common in this country but it may produce an eruption which can baffle the physician unless he is familiar with the lesions produced by iodine and its salts.

TREATMENT

Having diagnosed or suspected a drug eruption the only treatment usually required is to withhold the drug, when the rash will disappear more or less quickly. Treatment of the actual lesions, if any is required, is along normal lines, that is, it should be the same as for the natural lesions the eruption resembles.

More active treatment, however, is required for the more serious manifestations, such as exfoliative dermatitis which may follow the administration of one of the heavy metals, arsenic, gold, bismuth or mercury. *British anti-lewisite* (*BAL*) has proved of great value in these cases; it combines with the metal, even if it is intracellular, to form a harmless, easily eliminated compound. BAL is given intramuscularly in oily solution, and a normal procedure is to give three or four injections of 2 ml. of 5 per cent. BAL, at four-hourly intervals the first day, two injections daily for the next three days, and one injection on the two succeeding days. Naturally the patient must be kept in bed and otherwise treated *secundum artem*. At the other extreme the rash may be so slight or so controllable that the administration of the drug need not be interrupted. This is usually the case with the ninth day erythema sometimes seen during the administration of organic arsenicals, or when the use of penicillin is followed by urticaria. In this latter case the rash is usually abolished or minimized by one of the *antihistamine drugs*. There are instances, however, in which the necessity for continuing the drug, perhaps the only effective means of combating a condition dangerous to the patient's life, has to be balanced against the effects of the eruption. In such cases it may be justifiable to continue it if the skin condition is not in itself threatening the patient.

One last general consideration: a drug eruption may not appear until the drug has been stopped. This may be due to an accumulation of the drug within the body, as in the case of the iodides, or to the time lag in the production of an allergic reaction, as in the appearance of urticaria seven to fourteen days after the administration of penicillin.

DRUGS AND THE ERUPTIONS THEY PRODUCE

It is necessary now to consider the eruptions which may be produced by various drugs. It is not possible in an article such as this to give a complete list of either the drugs which may cause eruptions or of all the lesions of the skin which they have been credited with producing; only the commoner and more important will be dealt with. It must be remembered, too, that new eruptions due to, or supposed to be due to, drugs are constantly being described, as new drugs are introduced or fuller knowledge of the older ones is gained. I read in the daily press only the other day that an Australian cricketer had difficulty in batting owing to his hands peeling from the effects of penicillin given for tonsillitis; but perhaps the newspaper diagnosis was wrong and the desquamation was secondary to the disease and not to the cure.

Of the older drugs the *halogens* are important and the eruptions they produce are striking. To the uninitiated eye the lesions may appear too substantial to be produced by drugs. The eruption may not appear until the drug has been stopped and may be slow to clear, even taking months to disappear completely, and there may be residual scarring.

Iodide eruptions usually occur on the face and back. The lesions may be like acne or a pre-existing acne may be aggravated, but the typical eruption is papular, pustular or even granulomatous in character.

Bromides may also produce or aggravate an acne and a fixed bromide eruption has recently been described, but ulcerated, fungating lesions with marked crusting may occur.

Salicylates, aspirin and their derivatives may produce erythematous or urticarial rashes, or a fixed drug eruption, or erythema multiforme- or nodosum-like lesions.

Phenolphthalein has already been referred to. It typically produces a fixed drug eruption: medallion-like lesions, brownish in colour, sometimes more or less eczematized.

Barbiturates may produce morbilliform or purpuric lesions; bullæ may appear, especially on the mucous membranes. Fixed drug eruptions may occur. I recently saw a patient with a phenobarbitone rash of this type: she had lesions resembling lupus erythematosus on the face, and on the forearm a patch closely simulating ringworm, complete with vesicular border.

Arsenic.—Inorganic arsenic, if its use is long continued, leads to thicken-

ing of the skin, especially of the palms and soles. This keratosis may undergo malignant degeneration with the production of squamous cell epithelioma. There is often also a patchy or generalized darkening of the skin, a melanosis, which may lead to suspicion of Addison's disease.

Organic arsenic, like the other heavy metals, may produce an exfoliative dermatitis which may be fatal or lead to long-continued disability. Fortunately treatment with BAL has considerably improved the outlook. The erythema which occurs about the ninth day of an arsenic course is of less moment and, with care, treatment need not be interrupted.

Gold may give rise to an exfoliative dermatitis or to a lichenoid eruption with thickened, purple-brown lesions. The first sign of such sequelæ calls for the immediate cessation of treatment, but these lesions are helped by BAL.

Bismuth may give rise to a stomatitis; skin eruptions are less common but may occur. As with other heavy metals, BAL is useful.

Mepacrine colours the skin and conjunctiva yellow in all cases in which it is taken for a sufficiently long time, but this is of no moment. In exceptional cases it may give rise to a more or less generalized lichenoid dermatitis, resembling lichen planus but with more desquamation. The distribution is sometimes pellagra-like, on the exposed parts, and deep blue pigmentation may appear on the gums, hard palate and even the teeth, nails or the cartilage of the ears, nose or trachea.

Sulphonamides deserve special mention. Their widespread use and the great benefit following their proper administration in suitable cases tend to obscure the disadvantages attending their indiscriminate employment. Sensitization to sulphonamides is easily achieved, especially by their prolonged administration locally to an inflamed skin, and dermatologists are very chary of using them in this way. Once sensitized the patient remains sensitized more or less permanently to all drugs of this group and to their administration by any route. Occasionally the sensitization is specific to one member of the group and it may disappear spontaneously, but such cases are not common. The typical sulphonamide eruption is a more or less generalized dermatitis with sensitization of the skin to light, so that the eruption is worse on the exposed parts. This distribution often gives the clue to the cause of the dermatitis, and the extensiveness of the eruption and its aggravation on exposure to light may make the patient's condition a most miserable one. Sometimes lesions midway between erythema nodosum and erythema induratum occur. These eruptions usually call for withdrawal of all sulphonamides and their replacement, if necessary, by an antibiotic, but when medication by a sulphonamide is essential it can sometimes be continued by nursing the patient in semi-darkness. Desensitization to sulphonamides has been achieved by starting with a very small dose and gradually increasing it, but this cannot be done in a hurry, and if sulphonamides are required they are usually needed urgently.

Antibiotics are not such great offenders as the sulphonamides and it may

be necessary to consider carefully whether or not their administration cannot be continued, especially in view of the grave conditions for which they are usually employed. They may act as foreign proteins and their reactions often resemble those seen after the administration of serum. The latent period which may elapse before the rash appears may result in its delay until the drug has been stopped—an important point to remember.

Penicillin may give rise to urticaria, angioneurotic œdema, pruritus or other manifestations as seen in serum sickness, or to eruptions like those seen in some tinea infections, such as pompholyx of the hands and feet, which show the affinity between the moulds and the pathogenic fungi. Erythema nodosum has been reported and, but rarely, sensitization of the skin to light. Penicillin reactions may be immediate, as in those already sensitized, when they occur within twenty-four hours of its administration, or delayed, occurring seven to fourteen days later, as with other foreign proteins introduced into the body. Penicillin reactions, especially the urticarial ones, are usually controllable by antihistamine drugs, such as benadryl, and the treatment need not be interrupted.

Streptomycin may produce urticaria or stomatitis. A typical reaction is an erythematous, maculo-papular rash, usually itchy, which may occur on any part of the body. It is self-limited and lasts for five to ten days. Exfoliative dermatitis may occur. These reactions seldom happen if the daily dose of streptomycin is one gramme or less, and except in the case of exfoliative dermatitis do not call for cessation of treatment.

CONCLUSION

As time goes on and more and more active drugs are brought into use it becomes increasingly necessary to keep the possibility of drug eruptions in view. If a drug eruption is suspected the drug should be withdrawn, substituting another non-allied drug if necessary, when the rash, if due to the drug, will improve and may soon disappear. If the eruption is not of a serious nature the diagnosis may be confirmed by giving one dose of the drug, when the rash will return. The most serious result of administration of a drug is exfoliative dermatitis, and this must always call for immediate stoppage of the drug and the use of the most active measures available to control it. But the most useful advice with regard to drug eruptions, as with syphilis, is to keep them *in* one's mind but never *on* one's mind.

THE ANTIHISTAMINE DRUGS IN DERMATOLOGY

By E. J. MOYNAHAN, M.R.C.P.

Assistant Physician, Dermatological Department, Guy's Hospital.

THE antihistamine drugs are of importance in dermatology from two aspects: (1) therapeutic and (2) investigative. In the brief account which follows, emphasis will be on their therapeutic importance, although some reference will be made to investigative work with these drugs.

HISTAMINE

No account of the antihistamine drugs can be considered complete without some reference to histamine and its properties. Histamine (β-iminoazoyl-ethylamine), a decarboxylation product of histidine (although this is probably not how it is formed in the living animal), has no known physiological rôle in the normal animal, yet it possesses very powerful pharmacodynamic properties. These, which vary from species to species, consist of (1) an action on unstriped muscle, which responds with a powerful contraction; (2) an action on the capillaries, which it causes to dilate and also to increase their permeability; and (3) its marked secretogogue action, particularly on the gastric juice. In man, these effects can be demonstrated by the intravenous injection of a small dose of histamine. This is usually followed by bronchospasm and intense dilatation of the small vessels of the face and probably of the dura (which is believed to be the cause of the headache of a migrainous type that quickly follows the injection); there may also be a general vasodilatation in some subjects, leading to a fall in blood pressure, and syncope may be produced. There is also a marked increase in gastric secretion, as revealed by test meal, particularly of hydrochloric acid. Local injection or iontophoresis of histamine into the human skin produces the familiar "triple-response" of Lewis and Grant (1924).

Dale and Laidlaw (1910) first drew attention to the resemblance between these actions and anaphylaxis, but it was not until the antihistamine substances were discovered that the link between them was convincingly shown. All workers are now agreed that histamine is released in the course of anaphylactic reactions, and antihistamine drugs have played a large part in demonstrating its prominent rôle in anaphylactic and allergic phenomena. However, it should be borne in mind that histamine release will not account for all the phenomena observed in anaphylactic and allergic states.

Little is known of the form in which histamine exists inside the cell, but it is probably bound in some way to protein, and remains in this physiologically inactive state until it is released by some injury or other. The tissue content of histamine varies greatly, even in the same species; the lungs in

most mammals have a high content; the skin in man also has a relatively high content, 5 to 18 mg. per kg. (Bovet and Bovet-Nitti, 1948). Nothing is known of the precise significance of these differences in tissue content, but the high content of those tissues in contact with the environment of the animal, e.g. lung, skin and nasal mucosa, may be of importance in the defence of the animal.

Histamine is destroyed rapidly in the living animal by an enzyme *histaminase*, which is identical with, or closely allied to, diamine oxidase. The intestinal epithelium has a high content of this enzyme, which may be looked on as the natural antihistamine agent. A commercial preparation of the enzyme ("torantil") was given clinical trials some ten years ago, but the results obtained were not consistent, and in any case the synthetic antihistamine drugs have probably permanently superseded it, at least as therapeutic agents.

THE ANTIHISTAMINE DRUGS

It is not surprising that histamine held a particular fascination for pharmacologist and physiologist alike, and that a search was made for substances which would annul its effects. It was soon shown that many compounds, in particular amino-acids such as arginine and cysteine, possess some antihistamine activity, although this activity is very weak. Fourneau and his pupils, and later the workers at the Pasteur Institute in Paris, played a prominent part in the search for, and synthesis of, the antihistamine agents. Bovet and Staub in 1939 were the first to prepare a really active antihistamine substance when, in the course of their studies of the phenolic ethers, they discovered 929F (thymoxyethyl-diethylamine), which proved to be an active antihistamine agent, and was found to protect the guinea-pig against two to six times the lethal dose of histamine.

These substances were too toxic for clinical use, and it was not until the introduction of "antergan" in 1940, that the first synthetic drug with antihistamine properties suitable for clinical trial became available in France. The invasion of France interrupted this work, but it was resumed during the German occupation, and "neoantergan" (mepyramine maleate) emerged as a result of the work of Bovet and his colleagues. Since then research in different parts of the world has led to the discovery of many other substances which possess the property of inhibiting the action of histamine to a greater or lesser degree. These active substances do not possess a common chemical structure, and in fact they fall broadly into ten groups (Bovet and Bovet-Nitti, 1948).

In spite of their great diversity in chemical structure these agents exhibit a remarkable constancy in their pharmacological actions, the more important of which may briefly be summarized:—(i) They block the bronchoconstrictor action of histamine; (ii) they prevent the histamine contraction of the unstriped muscle of the gut and the uterus; (iii) they inhibit the vasodilator action of histamine; (iv) they reduce the permeability

of capillaries, irrespective of whether this has been increased by histamine or not; (v) they will prevent anaphylactic shock in certain species; (vi) they do *not* interfere with the secretogogue action of histamine on the gastric juice. Thus some animals succumb with perforated gastric ulcers, although they can otherwise be protected against huge doses of histamine. This may be of some importance in clinical practice, but no evidence has yet been produced that it is so.

As well as these antihistamine effects, the drugs also have other properties. They are good surface anæsthetics, and it has been shown that this property is quite independent of the antihistamine action. Some of these drugs are sympathomimetic whilst others are sympatholytic. They are also anti-acetylcholine agents, but their activity in this respect seems to vary inversely with their antihistamine effect. In man they have been shown to have a potent influence in certain of the allergic disorders, and they will abolish the histamine-induced triple response in human skin.

MODE OF ACTION

The way in which these drugs inhibit the action of histamine has not yet been determined with certainty. There are several possibilities: (i) they may prevent the liberation of histamine from the hypothetical protein-histamine complex in the cell; (ii) they may actually destroy histamine as it is formed or released, in much the same way that the enzyme histaminase behaves; (iii) they may combine with histamine after its release from the cell, and thereby inactivate it by forming a pharmacologically inert compound with it; or (iv) they may act as competitors with histamine for attachment to the cell receptor. The bulk of the evidence is in favour of the last view, and it is probable that they exert their action *vis-à-vis* histamine by preventing its access to the receptor in the cell. This hypothesis can account for the failure of the drugs to inhibit the secretogogue action of histamine on the gastric juice, which would be difficult to explain if one or other of the theories mentioned were true.

TOXICOLOGY

When taken in therapeutic doses, the antihistamine drugs are remarkably free from serious toxic effects. There is a considerable variation from person to person in the dose required to produce unpleasant side-effects, and even in a given individual's tolerance of different drugs in the group. No signs of damage to the blood-forming organs, viscera or the central nervous system have been observed, even in patients who have taken the drugs for periods exceeding a year. They are not habit forming, neither do they produce addicts. When given in toxic doses to animals, hyperexcitability, convulsions leading to coma and death have been the usual symptoms produced, in contrast to those commonly produced in human subjects, when sedative effects are the rule. The literature is full of reports of the side-effects which may accompany the taking of these drugs, and

brief reference will be made to these effects, but as a rule they are mild when they do occur, and one cannot help feeling that many authors have given undue prominence to these minor inconveniences, which most patients will cheerfully tolerate in return for the great relief obtained.

The most common and important side-effect is *drowsiness*, which has been reported in 16 per cent. of 5,615 cases treated in the United States with 8 different histamine antagonists (Loveless and Dworin, 1949). This symptom can be prevented, as a rule, by taking 5 mg. of amphetamine twenty minutes to half an hour before taking the dose of the antihistamine drug. Car drivers and others occupied in driving vehicles, as well as safety personnel such as signalmen, radio watchers, and the like, should be warned of the risk of drowsiness while taking these drugs. Aircraft pilots should not be allowed to fly while under treatment with antihistamine drugs.

Gastro-intestinal upsets are next in frequency, but are usually avoided if the drug is not taken while the patient is fasting.

Excitement, nervous irritability and *insomnia* sometimes follow the taking of these drugs, and thephorin is a prominent offender in this respect. "Dizziness" and headaches are not common, but have been reported.

In practice, it will rarely be necessary to discontinue the drug because of the severity of the side-effects. It often suffices if the dosage is reduced, or, if this does not help, another drug should be substituted. In patients who experience drowsiness after taking these drugs, it is often possible to exploit the soporific action of the drug to the advantage of the patient. Many patients are grateful for their hypnotic effect, as well as for their antipruritic powers, and the drugs themselves alone, or combined with phenobarbitone, the effects of which the antihistamine potentiates, may secure a good night's rest when other methods have failed.

The antihistamine substances can be applied to the skin in suitable bases. They are on the whole well tolerated by the skin, but sensitization does occur in a small number of cases. It should be remembered, too, that when they are incorporated in a penetrant base they are absorbed quickly, and side-effects will follow in susceptible subjects.

"HISTAMINOID" REACTIONS

Pellerat (*see* Huttrer, 1949) has drawn attention to the possibility that "histaminoid" reactions or accidents may become frequent following the introduction of the more potent antihistamine agents into clinical practice. The "histaminoid" reaction occurs as an acute asthmatic attack, which is precipitated by the taking of an antihistamine drug, usually for some allergic condition. In brief, the patient may be said to gain relief from his urticaria at the price of a sharp asthmatic attack. Pellerat has sought to explain these reactions in the light of his findings of the changes in the histamine content of whole blood and plasma, before and after taking an antihistamine preparation, both in the normal and allergic subject.

These consist of a marked increase in the circulating histamine following

the administration of the antihistamine drugs. This increase occurred irrespective of the route by which the drug was given. He explains the "histaminoid" reactions as follows:—

> The tissue histamine is displaced by the antihistamine drug from the cell receptor, and is released into the blood, where it may reach quite high concentrations. Now, it is well known that tissues differ considerably in their sensitivity to histamine, even in the same individual, so that if the same were true of the antihistamine drug itself, and if, for the sake of argument, it combines more with receptors in the skin than in the lungs, then the high content of histamine in the blood would be free to attach itself to the cell receptors in the bronchi, and thereby cause an asthmatic attack.

Little comment has been made on these findings of Pellerat, but it is not an uncommon experience, with some patients suffering from atopic dermatitis, to find that the administration of these drugs will cause the eruption to disappear, only to be exchanged for asthma. More investigation of this phenomenon, which often occurs without the intervention of an antihistamine agent, is needed, and there is no doubt that the advent of these drugs should enable us to gain a better understanding of this important subject.

MODE OF ADMINISTRATION AND DOSAGE

The antihistamine drugs can be given by intravenous or intramuscular injection, but they are usually taken by mouth. In dermatological practice they are often used as topical agents, and are incorporated in appropriate vehicles for this purpose. They possess an unpleasant taste and produce a local anæsthesia if they come in contact with the tongue or buccal mucosa; for these reasons they should be swallowed whole in pill or capsule form. The usual adult dose is 100 mg. every four hours, for all of the drugs which are available in Britain, except phenergan and thephorin, which are usually given in 25 mg. doses. No rules can be laid down about dosage in any given case; the practitioner will be guided by the clinical response to treatment and the patient's tolerance of the drug chosen. It is good practice to begin treatment with the standard dose of one of the active agents, e.g. anthisan or pyribenzamine, increasing the dose to the limit of tolerance. If the symptoms do not respond, then the more potent phenergan should be tried.

Children tolerate these drugs well, and the average child of twelve can take the full adult dose. The elixir of benadryl is the drug of choice for infants and toddlers. The dose will vary with the age of the infant, beginning with 30 minims (1.8 ml.), but this can be increased up to the limit of toleration. Small children are more likely than adults to become excited as the toxic dose is reached.

Proprietary creams and ointments containing these agents are usually well tolerated, both by children and adults. The creams, particularly if they are of the vanishing cream type, penetrate quickly, and may not be tolerated by the skin in cases which show considerable vesiculation or bullæ formation, and in some cases with fissures, e.g., in the natal cleft. Ointments are slower-acting and are often tolerated when the creams are not.

INDICATIONS FOR USE IN SKIN DISEASES

From theoretical considerations, the antihistamine drugs should be effective in conditions in which histamine release is the main feature, and, broadly speaking, this is true in practice. It should be remembered that these drugs are not "etiotropic", and do not in any way deal with the ultimate cause of the malady in which histamine is released. In the brief account which follows the maladies are classified with this in view.

(A) Disorders in which histamine release is probably the sole factor producing symptoms

(a) *Acute and chronic urticaria.*—All reports agree that the antihistamine drugs score their greatest dermatological successes in the management of these conditions. The cause should always be sought, and eliminated if found. Treatment with these drugs should be vigorous, and it would be almost true to say that there is no case of urticaria in which the eruption cannot be controlled, provided that the patient can tolerate the dosage required. Although this ideal cannot always be reached in practice, there is no doubt that many practitioners, by underdosage and by failure to change to a more potent agent when the weaker drug is ineffective, fail to get the best help from these drugs. In chronic and recidivant cases a common cause of disappointment is failure to persevere with treatment. The antihistamine drugs are without doubt the most effective agents we possess for the treatment of urticaria, and for this reason alone they deserve a high place in the dermatological pharmacopœia, but, precisely because of their success in controlling the eruption, they make it more necessary for the practitioner to discover the cause of the urticaria. In particular, he should always look for the occult systemic cause, such as leukæmia, and remember that intestinal and other parasitic infestations may present with urticaria.

(b) *Angioneurotic œdema.*—The antihistamine drugs are effective prophylactic agents for this condition, but should never be relied upon to produce rapid disappearance of existing lesions. Adrenaline should be used for this purpose and, if œdema of the glottis is endangering life, tracheotomy will be necessary.

(c) *Serum sickness.*—The antihistamine drugs are effective in the prevention and treatment of this condition. They should be given when serum reactions are anticipated.

(d) *Drug rashes and drug allergies.*—Histamine plays an important part in these conditions, and consequently the antihistamine agents are of great value in their treatment. The intense itching which may be present is usually well controlled by them. Penicillin urticaria is, as a rule, well controlled by these drugs. They should be given prophylactically to patients who are prone to develop urticaria following penicillin injection. They are very helpful in controlling itching and lichenification in exfoliative dermatitis due to arsenic or gold. The practitioner needs no reminding that treatment with BAL should begin promptly in these cases.

(e) *Urticaria due to infestation* with helminths such as tapeworms, will respond promptly to these drugs, only to return. This cause should always be borne in mind when relapses occur on stopping treatment.

(f) *Emotional ("cholinergic") urticaria.*—This rare form of urticaria, originally described by Grant and his pupils (1937), and usually precipitated by emotion or heat, responds well to antihistamine therapy. The patient, who knows the circumstances which produce an attack, can avoid one by taking the drug beforehand.

(g) *Urticaria pigmentosa.*—In this malady the drugs control the itching.

Satisfactory results have been reported in upwards of 75 to 80 per cent. of cases in the foregoing groups.

(*B*) *Ecto-parasitic infestations, in which histamine plays an important part in producing symptoms*

These comprise the common itching papules and other irritating lesions which accompany infestation by fleas, lice or the acari of scabies. The itching produced by these parasites is at least partly due to histamine released by tissue damage occasioned by the bite of the arthropod, and complete relief usually follows antihistamine therapy. It is needless to add that the offending invertebrates should be dealt with appropriately with DDT, gammexane or benzyl benzoate.

(*C*) *Bites and stings, in which histamine may be injected at the time of infliction, and also released from damaged cells in the skin of the victim, and is responsible for some of the symptoms*

The bites of mosquitoes, tabanid and other flies, and sandflies, as well as bee, wasp and hornet stings, are often relieved by local applications containing these drugs. This should be done as soon as possible after the sting has been inflicted. Anthisan cream proved effective in a small number of cases of wasp stings, last summer, including a personal experience of its value, when applied quickly. Thephorin ointment has a good reputation in America for these painful maladies (Strauss, 1949).

In groups B and C, 60 to 80 per cent. success may be expected.

(*D*) *Disorders in which histamine plays a subsidiary part in producing symptoms*

These include photodermatitis, sunburn, radiation injuries to the skin, minor thermal burns, chemical burns and contact dermatitis, in all of which the antihistamine drugs give some relief from itching. Further work is needed on the mechanisms underlying contact dermatitis before the rôle of these drugs in its management can be evaluated. Estimates of the success of the antihistamine drugs in this group average less than 50 per cent.

(*E*) *Disorders of unknown etiology, in which histamine plays a variable part in the production of symptoms*

(a) *Atopic dermatitis.*—As this condition is one of the allergic dermatoses, great hopes were held that the antihistamine drugs would prove as effective as with the urticarias. This hope has not been fully sustained, but the drugs

are of great help, if a little capricious in their action. This may well be due to variations in the histamine sensitivity of the skin, the causes of which are obscure. Many factors, other than histamine, influence this malady, so it is not surprising that treatment is difficult. In most cases the drugs can be relied on to give relief from itching, and local applications are also of great value. Histaminoid reactions may occur in these patients. It is difficult to estimate the degree of success which may be expected in these cases, but the drugs should be tried in every case.

(b) *Pruritus.*—The cause should always be sought, and when possible treated. Many cases benefit from antihistamine therapy, which should be tried as a routine. Results are far from constant. The same is true of localized pruritus of the vulva and anus.

(c) *Lichen simplex* (*neurodermatitis or lichenified dermatitis*).—Whatever the cause of this malady, there is no doubt that scratching plays a big part in the origin and perpetuation of lichenification. A vicious circle is established, wherein the trauma of scratching leads to further histamine release from the damaged cells, thus calling for a further bout of scratching to relieve the histamine-induced itching. The antihistamine drugs are of the greatest help in dealing with these very stubborn maladies. Dry eczematous conditions respond in the same way. Treatment may be oral or local.

(d) *Prurigo.*—This rare condition usually responds well to antihistamine therapy.

(e) *Lichen planus.*—Symptomatic relief is often obtained, but study of a controlled group is needed to assess the value of the drugs in curtailing the malady.

(*F*) *Conditions in which the rôle of histamine is undetermined, but in which good results have been reported in a proportion of cases*

These include dermatitis herpetiformis, herpes zoster, erythema multiforme and chickenpox.

CONCLUSION

The antihistamine drugs are among the most useful which the dermatologist possesses. It is too early to assign a definitive rôle to most of them. They are of even greater interest to the investigator, and for him they are valuable tools to enable him to understand the mechanism behind many skin disorders.

References

Bovet, D., and Bovet-Nitti, F. (1948): "Structure et activité pharmacodynamique des médicaments du système nerveux végétaux", Basle.
Dale, H. H., and Laidlaw, P. P. (1910): *J. Physiol.*, **41**, 318.
Grant, R., *et al.* (1937): *Clin. Sci.*, **2**, 253.
Huttrer, C. P. (1949): *Experientia*, **5**, 53.
Lewis, T., and Grant, R. (1924): *Heart*, **11**, 209.
Loveless, M. H., and Dworin, M. (1949): *Bull. N.Y. Acad. Med.*, **25**, 473.
Strauss, W. T. (1949): *J. Amer. med. Ass.*, **140**, 603.

CONTACT DERMATITIS

By H. R. VICKERS, V.R.D., M.Sc., M.B., M.R.C.P.

Consultant Dermatologist, Rupert Hallam Department of Dermatology, Royal Infirmary, Sheffield.

Of all the types of disease of the skin seen in the dermatological out-patient department, dermatitis is by far the most common and, fortunately, it is one of the most fascinating conditions for the dermatologist to treat. Although, by derivation, "dermatitis" should include all inflammatory reactions of the skin, over the course of years the word has been used to designate a particular type of reaction of the skin to some noxious agent coming into direct contact with the epidermis from without, or by the more indirect route by way of the blood stream and tissue fluids from within. No matter what the nature of this agent, the change produced in the skin is essentially the same. It is probable that the first reaction occurs in the prickle cell layer with damage to the cells. Resulting from this, the superficial vessels of the skin dilate and the patient sees an area of erythema which is often accompanied by that little understood sensation of itching. Shortly afterwards the epidermal cells become swollen with increased fluid; many burst and the fluid in the cellular layer passes to the surface and lifts up the horny layer, giving rise to vesicle formation. It is the formation of vesicles which is the hall-mark of dermatitis. Sooner or later, depending upon the severity of the response and the thickness of the horny layer, the vesicles burst, exuding serum giving the well-known weeping surface. From this stage the condition either heals by becoming scaly and gradually subsides or passes into the stage of chronic dermatitis in which the skin is red, thickened and easily aggravated by further contact with irritants.

This article is limited to contact dermatitis but, even so, in order to keep within reasonable bounds it is possible only to outline the main points of this type of dermatitis. Contact dermatitis, as the name implies, is that type of dermatitis occurring when the harmful agent attacks the skin from outside the body. It can be divided into two main groups, traumatic dermatitis and sensitization (contact) dermatitis. The essential difference between these two is that traumatic dermatitis is that produced by contact with some substance which would evoke a similar reaction in the skin of any other average individual, whereas sensitization dermatitis is that produced by contact with a substance to which the skin cells of the patient have become specifically sensitized and which does not produce dermatitis in an average normal person. Even though there is such a great essential difference between these two types of contact dermatitis, it is impossible clinically to differentiate the reaction produced.

TRAUMATIC DERMATITIS

Traumatic dermatitis is relatively uncommon, since people know by experience what substances must not be handled. As would be expected, the hands are most commonly affected and the eruption occurs characteristically in the interdigital surfaces of the fingers, on the backs of the fingers and hands and on both surfaces of the wrist. The palm and palmar aspects of the fingers, being protected by a thick horny layer, are not affected by any but the most drastic irritants. This type of dermatitis is seen commonly in washerwomen and charwomen and is due to the skin being constantly wet, often with a solution alkaline with washing soda or strong soap. Some of the new household bleaching agents and strong detergents are now causing traumatic dermatitis. The dermatitis occurring after contact with the alkaline cutting oil used by machinists is usually of this type, although occasionally a true sensitization is developed to cutting oil; grease and heavy oil are not in themselves harmful, but the skin is often damaged by the cleansing agents used after work. Traumatic dermatitis occurs in miners, at friction areas, the ankles, knees and waist line, as a result of damage to the skin by sharp particles of coal and stone dust being rubbed into the sweating skin by the overlying clothing. Alkaline cement dust is another common example of a primary skin irritant, producing dermatitis in builders and similar workers. These examples of traumatic dermatitis serve to illustrate the fact that any average normal skin is liable to break down on contact with such substances.

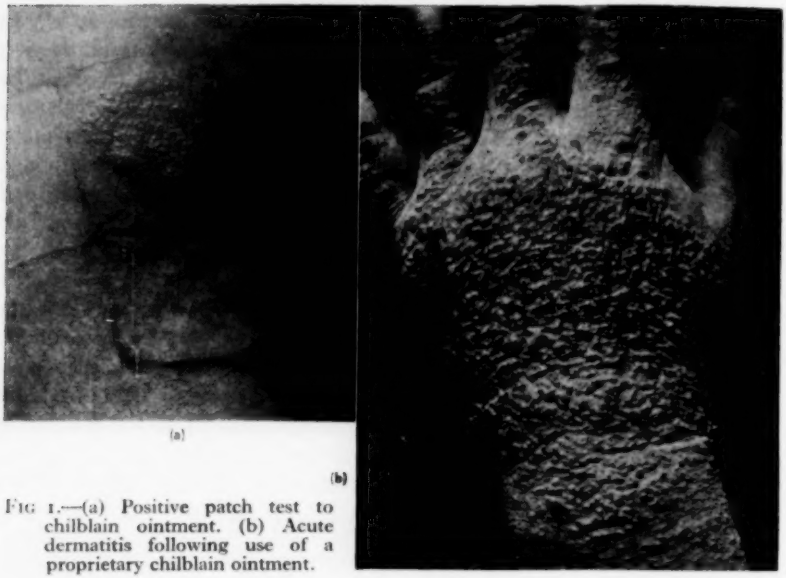
SENSITIZATION DERMATITIS

Sensitization dermatitis is much more common than the traumatic type, and successful diagnosis of the cause often requires all the detective powers that the practitioner has at his command. The establishment of cellular sensitivity is a fascinating but little understood subject. For the epidermal cells to become sensitized, the following factors appear to play a part:—

(1) Idiosyncrasy of the individual's cells.
(2) Contact with the sensitizing substance.
(3) The age of the patient.

The idiosyncratic factor is shown by the finding that some people are much more easily sensitized than others by contact with a particular substance. Whether or not the state of sensitization to a particular contact irritant can be inborn is unknown, but in most cases of sensitization dermatitis, careful history taking reveals some previous contact with the offending substance, and it is most probable that sensitization was then established. In all the cases I have seen, I have never been able to ascertain with certainty that previous contact with the substance causing the sensitization dermatitis was impossible, and if inborn sensitivity did occur, one would expect to see sensitization dermatitis not infrequently in children, but in practice this is extremely rare. Although many children nowadays are treated with medica-

ments which commonly sensitize the skin of adults, such trouble is never seen in children. I have been looking especially for such cases for several years and have only seen one case of sensitization dermatitis in a child; this was due to a proprietary chilblain cure used on the hands of an eight-year-old patient (fig. 1a and b). Thus it appears as if some hormonal influence occurring at puberty is also necessary for the establishment of sensitivity.



(a) (b)

FIG. 1.—(a) Positive patch test to chilblain ointment. (b) Acute dermatitis following use of a proprietary chilblain ointment.

It is also possible that some emotional upset may be necessary for easy sensitizability.

A further interesting fact found with the establishment of sensitivity is that although the offending substance may come into contact with only a small area of skin, such as a suspender buckle on the thigh, the whole of the skin becomes sensitized, so that any part of the skin which comes into contact with the substance will react by producing dermatitis and, what is more, in severe cases of sensitization, a minute amount of the substance absorbed through the skin, and thereby entering the blood stream, will produce a *secondary sensitization dermatitis* in any area with which it comes into contact. A striking feature of this secondary sensitization eruption is its almost perfect symmetry; the distribution of the rash on the two halves of the body is often a perfect mirror-image.

It is because of this generalized sensitivity of the skin cells that *the patch test* is of such value in elucidating the cause of these cases.

A small piece of the substance, suspected from the history as being a possible cause of the dermatitis, is applied to an area of apparently normal skin (on the arm

for convenience), covered with grease-proof paper or cellophane, and kept in place by adhesive plaster. Liquids are usually applied soaked in gauze, about the size of a postage stamp, in dilution such as would not affect a normal person's skin. Solids can be applied either *in toto* (such as suspender buckles), or shavings are applied on moistened gauze. In patients who are strapping-sensitive I usually keep the patch test in position with a "viscopaste" bandage. The patch is left on for forty-eight hours but removed earlier if the patient complains of severe irritation. If positive, the area of skin below the patch shows either erythema or vesiculation, the severity of the reaction depending upon the degree of sensitization. If negative, the skin is unchanged but should be examined for some days after the patch has been removed, since occasionally a delayed positive reaction appears (fig. 2).

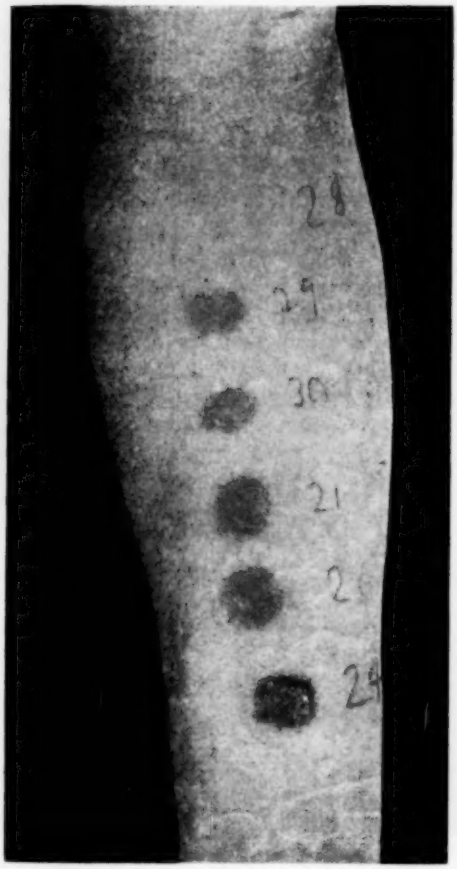


FIG. 2.—Multiple positive patch tests on the forearm of a man with "respirator dermatitis". The tests were to various stages in the manufacture of synthetic rubber and were kept in place for 48 hours by "viscopaste".

SOME CAUSES OF SENSITIZATION DERMATITIS

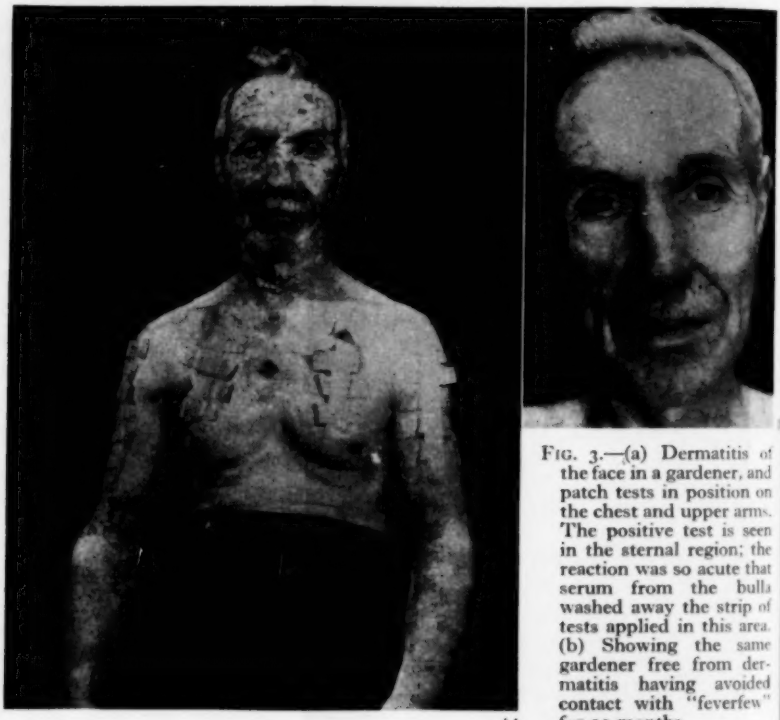
As regards substances which are capable of producing sensitization dermatitis, one might almost say that in a susceptible patient anything coming in contact with his skin for a sufficient length of time can give rise to sensitization dermatitis. Cases seen in out-patients' are usually caused by a member or members of the following groups: (1) plants; (2) medicaments applied to the skin; (3) cosmetics; (4) articles of clothing.

Of the *plants*, in this country, the *primula obconica* is probably the chief offender. Plants characteristically affect the eyelids, often giving such gross œdema that the patient has mechanical difficulty in opening the eyes, and on the hands and forearms linear streaks of dermatitis are often seen where the skin has been in casual contact with the leaves.

Several years ago, I was consulted by a keen amateur gardener whose life had

been a misery for the previous sixteen years because of chronic dermatitis of the face, neck, hands and forearms. Since the rash affected only the exposed parts I suspected some external contact irritant as being the cause, and I asked him to bring to me, in separate envelopes, a leaf of all the plants—including weeds—he had in his garden. To my horror he walked into the Department bearing some 90 labelled envelopes containing the leaves. With the help of the Sister, the next two hours were spent applying patches to his upper trunk and upper arms, but this proved to be a worthwhile task because when seen forty-eight hours later one of these tests—to a weed "feverfew"—was strongly positive, bullæ having appeared beneath this leaf. All the others were negative except chrysanthemum, which belongs to the same family as "feverfew", and this was slightly positive. He was instructed to avoid completely all contact with these two plants and he has remained perfectly well ever since (fig. 3a and b).

Medicaments applied to the skin are an increasing cause of sensitization dermatitis. Of these, sulphonamide is the worst offender and the most



(a)

FIG. 3.—(a) Dermatitis of the face in a gardener, and patch tests in position on the chest and upper arms. The positive test is seen in the sternal region; the reaction was so acute that serum from the bulla washed away the strip of tests applied in this area. (b) Showing the same gardener free from dermatitis having avoided contact with "feverfew" for 13 months.

dangerous. Sensitization to this group of drugs can be established by contact with the skin for only a few days, and once it is established, if in future the unfortunate patient is given a sulphonamide drug by mouth for some internal disease, the drug coming into contact through the blood stream with the sensitized epidermis causes a generalized severe dermatitis which, with the condition for which the sulphonamide was being given, may have

a fatal outcome. In addition, sulphonamide renders the skin more susceptible to the action of light, and since sulphonamides are not markedly better than other medicaments in treating various dermatoses, they should *never* be used locally in the treatment of skin disease. Penicillin cream and penicillin ointment are also giving rise to contact dermatitis, but in only a few cases are the patients sensitive to the penicillin; the sensitizing agent in most of the cases seems to be a combination of the ointment base and some breakdown product from the dermatosis treated. These cases do not as a rule give a positive patch test to the ointment base. Other applications commonly causing trouble are mercury, flavine, picric acid and various proprietary ointments containing local anæsthetics.

Cosmetics are not uncommon offenders. Face powder, lipstick, and hair dye are all sources of trouble and, in America, nail varnish seems to be responsible for some cases of localized dermatitis on the face, although I have never seen it in this country.

Articles of clothing, from fur collars and hat bands to shoes and nylon stockings, must all be considered. I recently was puzzled by a patient who had a very persistent dermatitis of her neck and lower face which cleared up in hospital but relapsed on discharge. Patch tests to her many coats and blouses were all negative, but eventually I found that she was extremely sensitive to the magenta areas of a multicoloured silk scarf, and the rash disappeared when she stopped wearing this.

FIG. 4.—Positive patch tests to spectacle frames; the frames were strapped on to the forearm for 48 hours.

Suspender buckles, brassière clips and straps and metal clips are frequent causes and we have recently had several cases of spectacle-frame dermatitis caused by sensitivity to the "plastic" type of frame (fig. 4).

DIAGNOSIS

Accurate and careful history taking is of the greatest importance in making the diagnosis. In the history, particular attention should be paid to the site of the first noticed eruption and to the time-relationship between contact with a possible irritant and the onset of the rash. It is unusual for there to be an interval of more than twenty-four hours between the appearance of the rash and contact with the sensitizing substance. As well as asking for possible irritants encountered at work, the patient's hobbies and home circumstances must be considered.

I recently saw a woman with a severe dermatitis of the exposed surfaces which was found to be due to sensitivity to the sawdust impregnated in her husband's clothing; his occupation was shaping the wooden handles of butcher's knives.

In examining the patient, the whole body should be seen, since patients often do not associate a recently acquired acute eruption with a chronic patch of dermatitis which they might have had for years and which they do not think is relevant to the history. Suspender dermatitis is often not mentioned in the history, perhaps through some feelings of false modesty.

Recently I was consulted by a patient with a severe dermatitis of her face and forearms which was proved to be a secondary sensitization dermatitis from contact dermatitis of the thighs caused by the metal of her suspenders, and which she had not mentioned in her history.

The site of the first appearance of the rash is of the utmost help in finding the cause; for example, the forehead and ears, often with gross œdema of the eyelids, are affected by hair dye, the eyelids by cosmetics and plants, lips by lipstick, neck by furs and necklaces, axillary folds (sparing the apices) by clothing dye, the back by brassière buckles, or straps, the genitals by contraceptives, the thighs by suspenders, and the feet and legs by shoe dyes. The diagnosis is confirmed by patch testing as described previously. In acute cases it is wise to wait until the condition is subsiding before applying the patch test, since the original eruption may be aggravated by the causative substance coming into contact with the skin.

TREATMENT

The most important detail in treatment depends upon accurate diagnosis of the cause, and it is essential to avoid all contact with the primary irritant. It is not yet known whether sensitivity, when established, persists throughout life. Prevention of noxious occupational substances from coming into contact with the skin is outside the scope of this article.

Local.—In the acute weeping stage the areas should be dressed frequently with wet dressings of a bland lotion. The skin is gently cleaned with the lotion and loose pieces of desquamated skin cut away, the lotion then being applied soaked in at least four layers of gauze and kept in place by loose bandaging. The dressing is changed often enough to be kept wet. In addition to calamine lotion, the following is helpful:—

Zinc oxide	1 ounce (28.4 g.)
Fuller's earth	1 ounce (28.4 g.)
Glycerin	½ ounce (14 ml.)
Water	to 12 ounces (340 ml.)

For the face, lead lotion is useful, and if the area is secondarily infected, the following are all good: (1) ½ per cent. silver nitrate solution in distilled water; (2) eusol solution; (3) mercuric chloride solution 1:4000; and occasionally I have had good results with wet dressings of penicillin lotion,

500 units per ml. As the condition subsides, calamine liniment or Lassar's paste is used, being applied three times daily, and the area cleaned with liquid paraffin if necessary before applying the new dressing. If healing is delayed and chronic dermatitis supervenes, tar in various forms often brings about complete cure. I often use Lassar's paste with ½ per cent. crude coal tar. I again stress at this point that sulphonamide ointments should *never* be used, and penicillin ointment and cream hardly ever.

Superficial *X-ray therapy* is of great value but should only be carried out by a skilled practitioner. Contrary to several authors, I find it of value even in the acute early stages, given in doses of the order of 50r (75 k.v.: 5 ma.), repeated if necessary weekly for three or four weeks. In the chronic stages I usually give 133r at fortnightly intervals for three or four times if necessary. Neither soap nor water should come into contact with the areas; soap because the alkaline content damages the already affected epidermal cells, and water because with loss of the horny layer the water comes into direct contact with the cells, and by osmosis the cells adsorb the water, eventually rupturing.

General.—In acute extensive cases, rest in bed materially shortens the course of the disease. Of drugs, adequate sedation is valuable; phenobarbitone in the usual dosage helps to allay irritation and so prevent the skin from being damaged by scratching.

Unless otherwise indicated, vitamin therapy does not help, and although some cases seem to improve with antihistamine drugs, it is not yet known whether this is a specific action or whether it is due to the sedative effect of these drugs. Dietetic restrictions play no part in the treatment, but alcohol, because of its action in causing peripheral vasodilatation, should be avoided. Many of these cases have some emotional disturbance which should be discovered and explained if possible, preferably by the dermatologist, since he is in a position to reinforce his mild psychotherapy with some practical method of treating the skin.

SUMMARY

This article is an attempt to explain shortly the factors responsible for dermatitis produced by contact with skin irritants, and a brief outline is given of methods of treatment which are known, by personal experience, to be effective.

Since the views expressed have been formed over the years, both from seed scattered by many sowers and as a result of personal management of patients, it is impossible to acknowledge any of these sowers except my original teacher, Rupert Hallam.

AN EVALUATION OF BARRIER CREAMS IN THE PREVENTION OF INDUSTRIAL DERMATITIS

By SIBYL HORNER, M.B., B.S., D.P.H.
H.M. Deputy Senior Medical Inspector of Factories.

To those who are relatively unacquainted with the subtleties of environmental medicine, the prevention of industrial, or in its wider sense occupational, dermatitis might seem to begin and end with barrier creams. The objective of this branch of medicine is prevention, and it is a fundamental axiom of industrial health that success will not be achieved unless everything that can be done *external* to the worker is first considered. This principle relates no less to the prevention of dermatitis than to the prevention of systemic occupational disease, such as aplastic anæmia from exposure to benzene, or encephalopathy from tetraethyl lead. Substitution of the offending substance by one less likely to cause injury is the first consideration, and, if this is not possible or practicable, "minimal contact" must be achieved by attention first to plant, technique and methods.

THE FUNCTIONS OF BARRIER CREAMS

Barrier preparations play a part in the prevention of occupational dermatitis, and their success or failure largely depends upon their fitment into the general measures of protection. It is only the necessarily exposed parts of the worker's skin to which barrier creams are intended to be applied before work, and well chosen protective clothing serves a dual purpose in protecting the worker's normal clothing and in limiting the length of contact between the skin and noxious substances; a very important factor in determining the onset of ill-effects. Barriers are often termed the "invisible glove", and their popularity thrives on the impracticability of wearing gloves in many industrial operations which call for speed and dexterity. Rubber gloves of a texture to withstand industrial usage are best reserved for work in which there is a serious risk from chemical or physical burns and from dermatitis, for which adequate protection cannot otherwise be given. Nothing can assail the prime importance of cleanliness in the prevention of occupational dermatitis, except the means which are sometimes taken to achieve this end—but more of this later.

Barrier substances are primarily used to reinforce and preserve the protective functions of the horn cells themselves, which with the natural secretions of the skin form the first line of natural defence against dermatitis. More rarely barriers may by their chemical composition modify the der-

matitis-producing features of the skin irritant encountered, but the design of barriers for this purpose is limited by the first essential that the protective coating shall itself be non-irritating when worn with the frequency and for the period of time demanded by industry. Ideally, too, barrier preparations should have a pH near to that of the skin—5.5 to 6.5—and prolonged application of a skin coating with higher values is unlikely to prove satisfactory. Another matter of some importance is the degree of solubility of the substances from which protection is sought in the barrier media. Cumming, Cameron, Cumming and Macraild (1947) described the tests made in the second world war in the search for an "ideal barrier" in which the nitrobodies in explosives causing dermatitis would be insoluble. Other tests made for the evaluation of barrier creams have been described by Sadler and Marriott (1946).

It should be possible to remove the barrier substance by ordinary methods after work, and it should not by its physical characteristics, such as greasiness, increase the danger or difficulty of the work to be performed. Barriers fall into three main groups: (a) water resisting, (b) oil resisting, which will also give some protection against industrial solvents, and (c) absorption resisting —the last for use when, as with nitrobenzene, trinitrotoluene, dinitro-orthocresol (an insecticide) and some compounds of mercury, there is in addition to a skin risk, a toxic hazard by skin absorption. Some evidence has been adduced that the presence of lanoline in a barrier preparation may promote skin absorption, and whether or not this is substantiated, great care must be exercised in the composition of barrier substances when there is a toxic hazard, to ensure that they will neither enhance the risk nor augment skin carcinogenic potentialities of certain substances, such as pitch, coal tar and mineral oil, with which there is contact in industry.

Within these three groups there is considerable scope for variation in the composition of the barrier, whilst for food manufacture special consideration has to be given to the property of some foodstuffs, particularly fats, of retaining the odours of barriers.

TYPES OF BARRIER PREPARATIONS

Emulsions—water-in-oil or oil-in-water—have overcome some of the disadvantages of the ordinary fatty ointments. Oil-in-water (the latter is the continuous phase) emulsions can be rubbed into the skin without leaving a greasy surface. They fill the follicles with emulsified material which, with the superimposed grime, easily washes out by ordinary methods. Lanette wax S.X.—emulsifying wax is the B.P. equivalent—is a mixture of sulphated higher alcohols, which, blended with fatty or paraffin bases, forms an O/W emulsion with large quantities of water. The cosmetic chemists have been astute in recognizing the virtues of emulsification, and to meet the industrial demand have led the field in producing a large variety of creams designed for particular needs, which are also acceptable to the worker. A skin preparation which does not appeal cosmetically to the worker, be it

a man or a woman, will rarely be successful however adequately it may have passed efficiency tests, for unless a protective cream is used consistently and is methodically applied with attention to detail, there is little chance of its proving a "barrier".

Schwartz (1942) describes six classes of skin protective applications, and he found that most of the barrier preparations in use in the United States were combinations of these.

(1) A simple vanishing cream which when rubbed into the skin fills the pores with soap which facilitates the removal of soiling when washing after work.

Type formula:

Stearic acid	20
Sodium carbonate	2
Glycerin	6
Water	78

(2) Ointments which leave a thin film of resin or wax on the skin and thus prevent the irritant from touching the skin. This class can be subdivided into (a) water-soluble films, and (b) water-insoluble films.

Type formula 2(a):

Acacia	5
Tragacanth	5
Borax	2
Water	88

Type formula 2(b)

Gum benzoin	5
Beeswax	2
Anhydrous lanoline	5
Ethyl alcohol	88

(3) Protective ointments which cover the skin and fill the pores with a harmless fat to repel water-soluble irritants and prevent the entrance into the pores of harmful petroleum oils, greases and coal tar derivatives.

Type formula:

Anhydrous lanoline	70
Castor oil	30
Perfume q.s.	

(4) Protective ointments which contain a non-irritant chemical intended to detoxify the industrial irritant.

Type formula:

Magnesium carbonate	5
Talc	5
Soap	30
Lanoline	30
Castor oil	28
Duponol	2
Perfume q.s.	

(5) Protective ointments which cause inert powders to adhere to the skin, forming a protective covering against skin irritants.

Type formula:

Zinc oxide	5
Talc	5
Iron oxide	1
Irish moss	2
Gum benzoin	2
Water	10
Alcohol	15
Vanishing cream	60

(6) Protective applications against the photosensitizing action of the heavy coal tar distillates, oil distillation residues and excessive sunlight.

Type formula:

Lanoline	58
Castor oil	30
Titanium dioxide	5
Methyl salicylate	5
Duponol	2
Perfume q.s.	

In this country there are numerous proprietary barrier preparations, to the compounding of the often complicated formulæ of which have gone much thought and pharmaceutical skill, with consideration both of the precise function the barrier is expected to perform combined with a high standard of acceptability to the user. Some ingredients of barriers chosen for their oil or solvent resisting properties may need to have oils and plastizers added to prevent surface disintegration, whilst for comfort and efficiency the composition of the barrier must allow for the passage or absorption of water vapour from the skin surface. Buffering agents are included in barriers to give better protection, and this is the rationale of the use of fatty creams in the presence of fat solvents, and for the addition of fats for soap formation in a cream designed to protect against alkalis. Substances such as menthyl or benzyl salicylate, titanium or magnesium dioxide are added to barriers to reduce radiation effects from ultra-violet light. Such radiation is well known to increase the skin-irritating properties of pitch and tar, whilst *in vitro* experiments have suggested that this is also true in the case of tetryl, which is converted by ultra-violet light to the more irritating methyl picramide which, with further irradiation, is decomposed (Brownlie and Cumming, 1946).

LEGISLATIVE AND OTHER REQUIREMENTS

The Pharmacy and Medicines Act 1941 requires a quantitative disclosure of composition in the case of any substance which is referred to in terms which are calculated to lead to the use of the substance for the prevention or treatment of any ailment, infirmity or injury affecting the human body. The composition of proprietary barrier creams is not printed on the container, but many of the manufacturers disclose their formulæ to interested members of the medical profession. The formulæ may be long and complicated, and the measure of success that these preparations has achieved is to a large degree dependent upon the precise methods of dispensing, and on their preparation in bulk aided by mechanical devices. There are three stages before the debut of a barrier preparation: First, with the precise purpose of the barrier in mind, a formula is evolved which must be made up and tested for a period for such disadvantages as mould growth and drying out. This is the pharmaceutical and ageing stage. After any necessary adjustments to perfect the first stage, the second stage is reached when efficiency tests are carried out on a laboratory scale. If these are satisfactory,

the final and most critical stage lies ahead—the trials of the barrier under industrial conditions.

Some time ago a Sub-Committee of the Pharmaceutical Society of Great Britain was appointed on the recommendation of the Minister of Labour's Advisory Panel on Dermatitis in Industry to submit formulæ for barrier preparations suitable for inclusion in the British Pharmaceutical Codex. The task of this Sub-Committee is a formidable one, but the last stage—practical trials of several barriers in industrial processes—is now in progress. In devising the scope and methods of these trials, statistical advice was taken, and of necessity some time must elapse before the stringent requirements have been satisfied. The objective of this scientific research is to devise basic formulæ for barrier preparations worthy of inclusion in the B.P. Codex, thus making them readily prescribable.

For some time reference has been made to barrier creams in departmental memoranda, and in placards for display in factories by the Factory Department of the Ministry of Labour and National Service, but the first mention of a barrier cream as a statutory requirement was in the Patent Fuel Manufacture (Health and Welfare) Special Regulations 1946, a Code which applies to the manufacture in factories of briquettes, ovoids or other blocks of fuel consisting of coal, coal dust, coke or slurry, with pitch as a binding substance. The short-term risk from this work is pitch "smarts" or dermatitis, and the long-term hazard is skin cancer. The specific requirement for the provision of a barrier cream is as follows:—

"The occupier of the factory shall provide for the use of persons employed in the factory, sufficient supplies of a suitable barrier cream or similar protective substance for the skin . . ."

Although not designated as a barrier preparation this is the purpose of the requirement of the provision of a "suitable ointment" in the Chromium Plating Regulations 1931 (which also apply to anodic oxidation by an electrolyte method). In these processes there is a risk of chrome dermatitis and of chrome ulceration of the skin and mucous membranes, and it is for the protection of the latter that a supply of ointment is required for insertion within the nostrils of the operative working at a bath. "Ointment" has also to be provided under the Herring Curing Welfare Orders, issued between 1920-27, and under the Chemical Works Regulations 1922. Several of the official placards (which must be displayed in certain factories) on the subject of dermatitis and chrome ulceration give a formula for a simple water-resisting ointment—3 parts of petroleum jelly to 1 of lanoline—which can be used either as a barrier or after work for maintaining the condition of the skin. When the nature of the work allows of it, a barrier of the water-resisting type with an oily base is generally preferable to those which may, in the long run, cause dryness of the skin.

BARRIER PROTECTION FROM MINERAL OIL

The efficacy of barrier creams in the protection of the skin against the

effects of contamination with mineral oil has for long been a vexed question, for by the nature of the work, involving, as it does, friction and the flow of oil over the exposed skin surfaces, it has not seemed likely that a barrier film would remain on the skin in sufficient quantity throughout the time of the working shift.

The Industrial Medicine Research Unit of the Medical Research Council, working at the Birmingham Accident Hospital under the direction of Dr. J. R. Squire, studied this question, and the results were published in a paper by Cruickshank (1948) on the "Evaluation of skin cleansers and protective creams for workmen exposed to mineral oil".

In assessing the value of cleansing agents and protective creams, tests were made of the fluorescence, under ultra-violet light, of oil persisting in the hair follicles after the use of these agents. Twenty-six barrier creams were examined, including samples of most of those in use in industry. Films of cream were applied to the extensor aspect of the forearm and then contaminated with machine oil, using untreated skin as a control. After washing, the fluorescence of the different areas was compared. Four out of six of the "soapy base" barriers tested afforded a fair degree of protection for a short time; all six of the "water-resisting" barriers were found to have some protective value: it was thought more by facilitating subsequent removal of the oil than by preventing physical contact of this with the skin. The "vanishing cream" type of barrier was found to be less effective than the "soapy base" type in preventing penetration of mineral oil on to the skin.

The four more successful "soapy base" barriers were found to increase in efficiency with an increase in the thickness of the film applied, but the films which were completely effective were too thick for practical use. A film of 120μ thickness (0.2 g. spread over 15.6 sq. cm.) allowed only very slight penetration, and was not too heavy for practical use. To afford complete protection a film of 190μ thickness (0.3 g. over 15.6 sq. cm.) was required, and this gave a "thick coating" to the skin. Films of 20μ thickness, which had some value for short exposures, were easily penetrated after exposure to mineral oil for periods exceeding 1 hour.

Dr. Cruickshank also tested the relative efficiency, in removing mineral oils from the skin, of cleansing agents varying from a 2 per cent. domestic soap solution to various soapless detergents. The mineral oils chosen for these tests were: (1) machine oil of viscosity 100 sec. Boventon-Redwood at 140° F. (60° C.); (2) cutting oil of viscosity 50 sec. Boventon-Redwood at 140° F. (60° C.); (3) "soluble" oil without the addition of water.

Cleansing agents tested were graded I, if, with a standard method of washing, they removed all three test oils. In this class were (a) soap powder 50 per cent. with wood flour 48 per cent., and two proprietary cleansers; (b) a mixture of soap and white spirit, and (c) a mixture of mineral oil, white spirit and sulphonated castor oil. A 50 per cent. soft soap (B.P.) solution and also soap powder, removed only cutting and soluble oil, whilst a 2 per cent. domestic soap solution failed to remove all three types of oil.

The immediate efficiency of various cleansing agents in removing mineral oil from the skin is not in doubt, but they will also degrease the skin, and over a varying period of time this is the disadvantage of powerful cleansing agents. Cruickshank found that washing for one minute with soap and water removed about one-fifth of the extractable fat from the skin, whilst washing with cleanser (c) above, for the same period, removed nearly one-half, and

approximately the same result was found with the soap-wood-flour cleanser. Although it was estimated that the natural fat of the skin may be re-formed in some four hours, it would seem reasonable to expect this function to deteriorate with prolonged usage of degreasing agents, and there is evidence from the chronic effects on the skin of trichlorethylene and of paraffin to show that this presumption is sound.

The only skin cleanser which is given "official" sanction for use when the skin is contaminated with mineral oil is sulphonated castor oil, 98 per cent., with a wetting agent (e.g. an alkyl sulphate), 2 per cent. This has proved of practical value, and it has not the great disadvantage of most chemical cleansers, i.e., of defatting the skin.

CHEMICAL CLEANSERS

This is the age of chemical cleansers of various compositions. Their advantage is that from the skin are thoroughly and quickly removed most greases, oils, paints, tar, resins and plastics—the contaminants for which soap and water is much less effective—whilst their disadvantage is in repeated degreasing of the skin. For some skin-irritating chemicals, such as alkalis, chromates, bichromates, sulphides, formaldehyde and the industrial solvents, cleansers of this type have no place. If one had to make a rule of thumb it would be to reserve the use of chemical cleansers for specific purposes when ordinary methods of cleansing are ineffective; bearing in mind that often the use of a suitable barrier before work will render unnecessary a special cleanser.

When the use of a chemical cleanser is indicated, one should be selected with the minimum risk from degreasing the skin; it should not be used in a greater strength than is necessary, and it should be thoroughly rinsed off after serving its purpose.

ROUTINE INSPECTION OF WORKERS

The prevention of dermatitis is unlikely to have its full measure of success unless, in addition to the proper use of barriers and cleansing agents in conjunction with practical adaptation of the principles of "minimal contact", there is also a carefully carried out periodical inspection of those engaged in work with a potential dermatitis hazard. This inspection is perhaps the sounding board for assessing the success and the use that is being made of all the other precautions. Should anyone show the early signs of skin irritation it is possible at this stage to institute treatment, which usually involves removal from contact for a while, and the prospect of an eventual return to the same work is in this way much enhanced. Inspection of personnel, which should be carried out on the job, can be effective if carried out by an industrial nurse, a well-trained first-aid attendant, or even by an intelligent supervisor, provided that ultimately the advice of a doctor with industrial experience is available.

The right treatment of dermatitis in its early stages will do much to prevent the chronicity of dermatitis which is largely responsible, together with the risk of recurrence, for the dread in industry of this condition. The mental attitude of the sufferer from industrial dermatoses must be appreciated from the outset. It is claimed by Halliday (1944), and supported by Robertson (1947), that there is a peculiar state of mind which is a predisposing factor in the causation of industrial dermatoses, and there is little doubt that a poor state of nutrition, anxiety not necessarily associated with the fear of skin disease, and home conditions which for one reason or another are not congenial, tend to heighten the susceptibility of the skin to external irritants.

CONCLUSION

This brief description of the ways by which the incidence of occupational dermatitis may be reduced indicates the small but important part now served by the proper use of well-chosen barrier preparations.

New lines of research are developing which may perhaps enlarge the scope of barriers in the industrial field. For example, the part played by the unsaturated fatty acids, linoleic and linolenic acid, in the metabolism of the skin has yet to be fully explored in the therapeutic field, and it is possible that these substances may help in the prevention of dermatitis by assisting the skin to maintain or recover its equilibrium in the face of repeated attack by the noxious substances of industry. With this aim in view linoleic acid is included in one of the proprietary barrier preparations.

MacKenna (1948), in a study of the evolution of slowly developing contact dermatitis, calls attention to the "quite heroic attempts" made by the epidermis in all cases of contact dermatitis caused by sensitizing agents. He points out that it is from the most highly organized cells in the epidermis that the horny layer is formed, and it is these cells which endeavour to protect the damaged area by the formation of a carapace which persists for a longer or shorter period, depending upon the amount of damage the epidermis has sustained. With growing knowledge of the biochemistry of the skin and of its complex reactions to environment, new stimulus and meaning may be given to the established methods for the prevention of occupational dermatitis.

References

Brownlie, I. A., and Cumming, W. M. (1946): *Biochem. J.*, **40**, 20.
Cruickshank, C. N. D. (1948): *Brit. J. indust. Med.*, **5**, 204.
Cumming, W. M., Cameron, M. C., Cumming, E. B., and Macraild, M. C. 1947): *Ibid.*, **4**, 237.
Halliday, J. L. (1944): *The Practitioner*, **152**, 6.
MacKenna, R. M. B. (1948): *Proc. IXth Int. Cong. indust. Med.*, 394.
Robertson, G. G. (1947): *Lancet*, **ii**, 4.
Sadler, C. G. A., and Marriott, R. H. (1946): *Brit. med. J.*, **ii**, 769.
Schwartz, L. (1942): *Med. Clin. N. Amer.*, **26**, 1195.

EMERGENCY TREATMENT OF APOPLEXY

By GEZA DE TAKATS, M.D.
AND G. W. GRAUPNER, M.D.
From the University of Illinois College of Medicine, Chicago.

THE attitude of the medical profession towards strokes has become one of nihilism. This situation has arisen for several reasons: (1) there has not been a systematic effort to separate the three major causes, namely embolism, thrombosis, and hæmorrhage, from each other, although this can be done in most instances; (2) the cerebral damage has been thought to be permanent, irreversible, and unalterable; (3) some patients have made such a good recovery without specific treatment except good nursing care that any therapeutic attempt has been regarded with suspicion, and thought to be superfluous and not responsible for the spontaneous improvement.

It is difficult to estimate the number of strokes occurring day after day, but the tremendous amount of residual damage following apoplexy is obvious to everyone. At St. Luke's Hospital, Dr. Gilbert and one of us studied 121 patients with apoplexy between 1940-46, and found 15 cerebral

TABLE I
SUMMARY OF FINDINGS IN 121 CASES OF APOPLEXY

	Diagnosis		
	Embolus	Hæmorrhage	Thrombosis (cerebral softening)
Number of patients	15	53	53
Average blood pressure	143/85	213/120	166/97
Sudden onset, per cent.	100	92	47
Normal spinal fluid, per cent. ..	100	30	90*
Improvement noted, per cent. ..	40	9	38
Mortality, per cent.	40	77	24

* No blood, but increased pressure due to hypertension.

emboli, 53 cerebral thromboses, and 53 cerebral hæmorrhages (de Takats and Gilbert, 1948). Table I indicates our diagnostic criteria based on this material.

CEREBRAL EMBOLISM

Cerebral embolism was diagnosed in patients with sudden cerebrovascular insult, who had an obvious cardiac lesion for the source of the embolus, or who had had previous embolic episodes to the brain or elsewhere in the body, whose spinal fluid was clear and showed no elevation of pressure.

The ages in this series of patients varied from eighteen to sixty, the average being fifty-three years. The blood pressure varied from 110/80 to 210/100 mm. Hg. Seven patients belonged to the hypertensive arteriosclerotic group, and 8 to the rheumatic group. Of the 6 patients with cerebral emboli based on rheumatic heart disease only 1 died, a forty-year-old male with heart failure; of the remaining 9 patients having cerebral emboli as postcoronary complications and hypertensive cardiovascular disease, 5 died. Although this is of no statistical significance in such a small series, it is obvious that the prognosis is better in the rheumatic group.

CEREBRAL THROMBOSIS

Cerebral thrombosis, or more appropriately cerebral softening, shows areas of malacia or necrosis in the brain as a result of stenosis or hyalinization of arterioles, whereas an arterial thrombosis is seldom encountered. In this group of 53 patients, 9 died in the attack. A fall in blood pressure and the anoxia of the inevitable broncho-pneumonia of the unconscious patient seemed to transform the silent or latent cerebral softening into the clinical entity of "thrombosis", or even death.

To make a diagnosis of encephalomalacia—not embolus and not hæmorrhage—we postulate a patient afflicted with cardiovasculo-renal disease, moderate hypertension, and an onset which is often gradual. Whilst loss of consciousness was present in approximately one-half of the cases, it did not persist for many days. Increased intracranial pressure was not observed, the spinal fluid was clear, and if the pressure of the spinal fluid was elevated, it was part of the hypertensive encephalopathy. This group is really diagnosed by exclusion of embolism and hæmorrhage from the causes of stroke.

The average age of this group was 60.8 years. The average blood pressure need not be stressed, since the study of the charts revealed that readings were determined at various stages of the attack and are therefore meaningless. It is an interesting fact, however, that postoperative or postcoronary hemiplegias were noted to be accompanied by a prolonged and rapid fall in blood pressure. This was also true in some strokes occurring during sleep. The onset was sudden in 25 and gradual in 28 of the patients.

If the patient did not die of the attack or of complicating broncho-pneumonia, recovery was slow, improvement being noted in 20, and no improvement in another 20 patients. Fatalities were recorded in 13 patients (24.5 per cent.), all of them dying between the fifth and twenty-eighth day after the accident.

CEREBRAL HÆMORRHAGE

Cerebral hæmorrhage was diagnosed in 53 patients; of these 41 died within a few hours or days, a mortality of 77 per cent. The average age of this

group was 58.9 years, ranging from forty-one to eighty years. The average blood pressure was 213/120, with extremes of 300/150 to 120/70. Again it should be pointed out that the vascular insult itself may modify the blood pressure readings, but the tendency for the highest pressures among the three types of apoplexy is well defined in cases of hæmorrhage. Only a few patients showed a gradual onset, but even in these a deepening coma was observed. A sudden fulminating onset was observed in 49, or 92 per cent. of the patients. The spinal fluid was clear in 30 per cent. Over two-thirds of the patients had bloody spinal fluid and three-fourths had bloody spinal fluid or increased spinal fluid pressure (over 160 mm. of water). In massive hæmorrhage the outlook was poor, only 9 per cent. improving; 14 per cent. were unimproved, and 77 per cent. died (table 1).

Attention should be called to the fact that in non-fatal hæmorrhage the spinal fluid may be free of blood in one-third of the cases, and the pressure is not elevated in one-fourth of the cases. On the other hand, in patients with cerebral softening the spinal fluid pressure was increased in 10 per cent. of the cases, due to hypertension. A second spinal tap done four to five days after the original insult may reveal red cells, frank blood, or increased pressure in patients with a slow leak of their intracerebral hæmorrhage in the ventricular system or to the surface of the brain.

There may, of course, be other reasons for acute cerebral anoxia, such as a long-lasting nitrous oxide anæsthesia with insufficient oxygen supply, or a prolonged operation on an exsanguinated individual, on a blue baby, or on hypertensives used to higher pressure. With the advent of the long-lasting operations, with or without profound loss of blood, the involvement in cerebral circulation must be considered.

LOCALIZATION

From the standpoint of localization it should be remembered that the majority of vascular accidents occur in the region of the internal capsule, from where the motor, the sensory, and visual phenomena originate. The lesion in the basal ganglia affects the extrapyramidal system and thus is responsible for the rigidity of the hemiplegic limb. The cortex itself may only be involved in collateral œdema and produce flaccidity. Flaccidity followed by spasticity means the disappearance of cerebral shock and is the expression of the actual organic damage. We shall see that in our therapeutic attempts this phenomenon is of significance.

The internal capsule is supplied by the perforating branches of the middle cerebral artery, which have been compared to the bristles of a beard. These are the vessels most often involved in a cerebrovascular accident and, depending upon the extent of hæmorrhage or softening, there will be contralateral hemiplegia, sensory changes, facial changes and sometimes ipsilateral involvement. It is well for all of us treating cerebral vascular lesions to have at least a rough conception of the area involved.

OUTLINE OF TREATMENT

The earlier treatment is begun the better are the chances for hastening restitution. A brief cardiovascular and neurological examination is done and the history is obtained from the relatives. The patient is immediately placed in an oxygen tent; this not only helps his anoxia but may indirectly aid his aortic depressor and carotid sinus reflexes. If signs of increased cerebrospinal pressure are dominant, a spinal tap is done and spinal pressure is measured. Frank blood indicates cerebral or subarachnoid hæmorrhage. Marked hypertension with signs of increased venous pressure in the neck requires venesection, which is done slowly, not more than 300 ml. of blood being removed at one time. Unless coma is deepening and a terminal condition is obvious, and if massive hæmorrhage can be reasonably excluded, a sympathetic block is performed with the patient in the reclining or semi-sitting position in his bed.

For diagnostic and therapeutic purposes we have generally preferred the anterior approach to the sympathetic chain. The method used is as follows:—

> The patient's neck is slightly hyperextended by placing a small pillow under the shoulder blade of the same side; the head is turned away from the site of injection. With an applicator dipped in iodine, a line is drawn from the mastoid process to the clavicle, through the tips of the palpable transverse processes. A dermal wheal with 1 per cent. procaine (without epinephrine) is placed over the tip of the seventh transverse process. A 4-inch (9 cm.) 22-gauge needle is inserted through this wheal. It must shortly make contact with the tip of the transverse process, which is quite superficial. Then the needle slides along the superior border of the transverse process until it contacts the body of the sixth cervical vertebra. Aspiration is now made for air-bubbles, for blood, and for spinal fluid: if this is negative, 10 ml. of 1 per cent. procaine solution are injected, aspirating repeatedly during this procedure.

A successful block must be followed within ten to fifteen minutes by a Horner's syndrome, by a dilatation of the conjunctival vessels, by a dryness and increased warmth of the face and ear lobes on the injected side, and by a rise in temperature and dryness of the corresponding upper extremity. Unless a Horner's syndrome develops, the injection must be regarded as faulty and should be repeated.

This cervical injection is done on the side of the lesion; this is not immediately obvious when the patient is seen quite early, since he may be quadriplegic and have a flaccid paralysis, although either a facial involvement or a beginning sensory change may point to the site of involvement. Dilatation of the pupil is more frequent on the contralateral side. Loss of pupillary reaction is again more frequent in hæmorrhage.

If improvement is to follow cervical sympathetic block, it should be noticed within the next ten minutes. The improvement may then continue, and should a relapse occur, the patient must be re-injected. We have not given these injections more often than once every twenty-four hours, but they might be given eight or twelve hours apart if improvement is followed

by signs of deterioration (table 2).

TABLE 2
APOPLEXIES: CRITERIA OF IMPROVEMENT FOLLOWING STELLATE BLOCK

	Number of Patients
Regained consciousness	6
Regained speech	5
Improved speech	12
Motor improvement	8
Abolished flaccid paralysis	10
No improvement	9

A total of 105 injections has been given to 50 patients. More than half of these patients received only one injection, since in our early experience we were not sufficiently aware of the importance of re-injecting the patient if the first injection seemed useful. To-day, it is customary to inject the cervical sympathetics daily until no further improvement is noted. It also seems that bilateral sympathetic block is more effective, at least in the animal experiment, but only a few simultaneous injections have been made in this series.

The time factor.—Gradually we have come to recognize the fact that, at least in the big cities, the patient must actually be in the hospital for some other reason when the cerebrovascular accident occurs, so that the injection can be given immediately. Of the 5 patients injected within the first hour,

TABLE 3
RESULTS CORRELATED WITH THE TIME ELAPSED BETWEEN ONSET AND STELLATE BLOCK

	Number of Patients	Improvement
First hour	5	4
2 to 6 hours	8	6
6 to 12 hours	7	5
12 to 24 hours	5	3
24 to 48 hours	20	3
More than 48 hours	5	0

1 was a visitor, 1 a blue baby who developed a hemiplegia during the exposure of the tetralogy of Fallot, 1 was in the hospital for coronary occlusion, and 2 had previous peripheral emboli and were fibrillating (table 3).

DISCUSSION

In spite of the theoretical considerations which made it seem unlikely that

the temporary elimination of vasomotor tonus of the cerebral vessels would effectively influence the deranged cerebral circulation following apoplexy, our clinical observations leave no doubt that in properly selected cases injected at the earliest possible moment, an acceleration of the phase of restitution may be expected. By this we mean that in all cerebrovascular accidents, surrounding the ischæmic or hæmorrhagic infarct, there exists a zone of stasis, vaso-paralysis, and exudation of plasma. This has been seen in the experimental animal through a window in the skull by Villaret and Cachera (1939). They also demonstrated the development of a collateral network around the infarcted areas and the existence of segmental spasms and dilatations in the non-obstructed vessels. They showed that these functional changes must be activated by an irritative sensory lesion of the obstructed vessels, since air embolism, whilst producing complete vascular block, was never accompanied by such phenomena. Their observations, however, relate to the vessels of the pia, which are known to have more vasomotor control than those of intracerebral vessels.

A second observation, which indicates the widespread cerebral damage a great distance from the original lesion, can be found in the histological studies of Evans and Scheinker (1944), who found diffuse cerebral atrophy accompanying focal injuries in head trauma. They reported that the white matter stands the collateral œdema and stasis much more poorly and that the hypoxia here is followed by diffuse gliosis. Although recently there has been a tendency to minimize the importance of cerebral swelling in concussions, the accurate measurement of White, Brooks, Goldthwaite, and Adams (1943) showed that œdema and congestion are present, due to extravasation of fluid through permeable anoxic capillary membranes. The question then arises, can sympathetic block relieve such stasis by (1) releasing the arteriolar spasm proximal to it; (2) improving venous drainage and thereby also decreasing intraventricular and intraspinal pressure; or (3) by so affecting the extracerebral portion of the carotids that more blood may be brought to the brain (Schneider and Schneider, 1934)? Such studies are now under way.

Additional evidence that sympathetic block radically changes the function of the brain following a vascular accident is provided by electro-encephalograms taken before and fifteen minutes after a successful block in a case of cerebral thrombosis. It has been noted that the slow foci in the left frontal, right frontal, right temporal, and right anterior temporal leads have all been accelerated and have taken on a normal pattern.

PLAN OF TREATMENT

On the basis of our conception, the following therapeutic measures seem indicated in acute cerebrovascular accidents:—

(1) In patients with cerebral embolism, an oxygen tent, medication for slowing of rapid fibrillation, stellate block, and anticoagulants are ordered.

Dicoumarol may be kept up for weeks and months according to a schedule we have discussed elsewhere.

(2) In patients with cerebral thrombosis, an oxygen tent, venesection in case of hypertension, stellate block, and release of increased spinal fluid pressure are indicated.

(3) In patients with cerebral hæmorrhage, an oxygen tent, slow spinal drainage, and neurosurgical consultation for possible evacuation of clots may be considered. No sympathetic block need be done.

In all three types of apoplexy, hypertonic sucrose or concentrated albumin with 5 to 7½ grains (0.32 to 0.5 g.) of aminophylline given intravenously should improve the cerebral œdema. There is some evidence that aminophylline lowers spinal fluid pressure, and its use seemed to us more rational than the extreme dehydration advocated in patients with cerebrovascular accidents or with head trauma.

SUMMARY

Attention has been called to the importance of a differentiation between cerebral embolism, thrombosis (or softening), and hæmorrhage. The importance of collateral stasis, vaso-paralysis, and œdema accompanying the cerebrovascular accident has been stressed. In 50 patients the cervical sympathetic trunk was blocked with procaine on the side of the apoplexy. Good response was obtained in 41 of these. Regaining of consciousness, of speech, motor improvement, and conversion of flaccid into spastic paralysis were also observed. Other methods of combating cerebral œdema and stasis may be added. A less passive attitude in the treatment of apoplexy is suggested.

References

de Takats, G., and Gilbert, N. C. (1948): *J. Amer. med. Ass.*, **136**, 659.
Evans, J. P., and Scheinker, T. M. (1944): *J. Neurosurg.*, **1**, 306.
Schneider, H., and Schneider, D. (1934): *Arch. exp. Path. Pharmakol.*, **175**, 606.
Villaret, M., and Cachera, R. (1939): "Les embolies cérébrales", Paris.
White, J. C., Brooks, J. R., Goldthwaite, J. C., and Adams, R. D. (1943): *Ann. Surg.*, **118**, 619.

ARTIFICIAL PNEUMOTHORAX

By NEVILLE C. OSWALD, M.D., F.R.C.P.

Assistant Physician, St. Bartholomew's Hospital, and Brompton Hospital.

RECENT knowledge of pulmonary tuberculosis is in danger of becoming lost in a fog of statistics. So often, the figures most acceptable to statisticians are the least comprehensible to clinicians who, although realizing their importance, cannot be expected to remember them in more than their broadest outlines. In this way we know that the mortality rates per million of the population have fallen in the last hundred years to one-sixth of their former level, and continue to fall at the rate of rather less than 2 per cent. per annum, there being little increase in the rate of fall in the last twenty-five years which might have been accounted for by the introduction of collapse therapy on a large scale. In recent years the decline in mortality amongst young female adults has lagged seriously behind the other groups, and there has been a relative increase in the incidence of the diseases in middle-aged males. The predominance of male to female cases, in the ratio of 4 to 3, continues (Registrar-General's Statistical Review, 1939). About one-half of all patients notified, and it is likely that not more than 10 per cent. of cases escaped notification, die from the disease within ten years of notification, and very few after that length of time (Stocks, 1944). These generalizations emphasize the two outstanding statistical features of pulmonary tuberculosis, namely, its steady decline as a cause of death and the high fatality rate amongst those affected by it.

Collapse therapy of some sort is now performed on about one-half of all patients treated in institutions for the tuberculous and undoubtedly has a favourable influence upon the course of the disease (Simmonds and Martin, 1948). During the past decade much useful statistical information has been recorded concerning the immediate results of artificial pneumothorax, but inevitably, long-term follow-ups have been jeopardized by the exigencies of the war.

CLASSIFICATION OF CASES

In order to assess the possible benefits of such treatment, some gradation of cases is necessary. To this end the most important prognostic features, namely the general condition, the extent of radiological changes and the presence or absence of demonstrable tubercle bacilli, have been combined in a simple classification, A1, A2, A3, and B1, B2, B3, according to whether or not tubercle bacilli have ever been demonstrated and whether the infection is slight, moderately advanced, or far advanced. This classification, which has been generally adopted since the early 1930's, forms the only real basis for comparison between groups of cases of pulmonary tuberculosis under varying conditions and forms of treatment. As pulmonary tubercu-

losis runs such a protracted course, a standard follow-up is desirable. Five-year mortality rates have steadily gained in popularity, in the knowledge that the great majority of deaths from pulmonary tuberculosis occur within five years of diagnosis, and that longer periods tend to increase the number of cases lost sight of. Where collapse therapy is concerned, controls must be derived from the same source as the treated cases, and be similar in other respects if any general prognostic conclusions are to be drawn; a glance at the five-year mortality rates for Midhurst Sanatorium (Trail and Stockman, 1932), the London County Council (Macnalty, 1932), the Reading district (Tattersall, 1947), and an industrial area in the North of England during the years of depression (Thompson, 1943), show how much the prognosis varies with social and economic circumstances, quite apart from any modifications which an individual form of treatment might produce.

CHOICE OF CASE

Before undertaking so tedious and time-consuming a measure as an artificial pneumothorax, a number of factors must be taken into consideration in each case, such as age, sex, general condition, possible pregnancies, and the availability of skilled treatment after leaving the sanatorium. In practice, nearly all patients are in a moderately or far advanced stage of the disease with demonstrable tubercle bacilli in the sputum at the time of induction (Bentley, 1936; Edwards and Lynn, 1939; Clarke and Erskine, 1940; Edwards *et al.*, 1944), the so-called groups B2 and B3. In the last resort, the determining factor must be the radiological appearances, in which account is taken of both the *infiltration and cavitation*. A review of 200 consecutive admissions to a chest hospital during 1945-47, treated by artificial pneumothorax, revealed the following radiological indications:—

Infiltration and cavitation	66 per cent.
Spread of infiltration under observation	25 per cent.
Failure of infiltration to resolve	7 per cent.
Spread of infiltration from opposite lung	2 per cent.

Two-thirds of the cases had proceeded to cavitation, which is rather less than the 88 per cent. of 400 cases reported by Clarke and Erskine (1940), and 95 per cent. of 393 cases submitted to Wollaston (1947) for thoracoscopy. It is evident that excavating lesions form the most common indication for artificial pneumothorax; experience has shown that healing is often dramatic if a satisfactory collapse can be obtained, and far more certain than the tedious months of inertia imposed by rest alone. Doubtless the infiltration in many of these was such as to merit artificial pneumothorax for itself, but the added cavitation made collapse doubly necessary.

In the second group, namely spread of *infiltration under observation*, the infiltration varied from a "minimal" lesion to extensive infiltration of the whole lung. These two groups together comprise over 90 per cent. of the cases and clearly show that artificial pneumothorax is undertaken, almost always, either in order to close cavities or else to control infiltration, whatever

the extent, which shows radiological evidence of progression.

That the disease should be unilateral is not of prime importance; in 64 per cent. of the present series the disease was bilateral, which is similar to the 59 per cent. of 557 cases submitted to thoracoscopy by Watt (1947).

Chances of obtaining artificial pneumothorax.—Artificial pneumothorax fails completely on account of pleural adhesions in about one-quarter of all cases (Trail and Stockman, 1932; Clarke and Erskine, 1940). Of the remainder, the shorter the duration (Clarke, 1940), and the less the extent of the disease (Edwards *et al.*, 1944), the greater the chances of obtaining a satisfactory collapse. Before the days of thoracoscopy and with the aid of phrenic avulsion, Clarke and Erskine (1940) were able to achieve a satisfactory collapse with control of the underlying disease and cavity closure in a third of their cases.

Thoracoscopy and division of adhesions.—The series of Brock (1938), Edwards and Lynn (1939), Barclay (1943), Edwards *et al.* (1944), Laird (1945), Watt (1947), and Wollaston (1947), comprise between them some 2,500 pneumothoraces. The adhesions were completely divided in 48 per cent., and were inoperable in 12 per cent. Among the intermediate 40 per cent., there is a diversity of classifications, but more than half were given a satisfactorily functioning pneumothorax. It is not possible from these figures to assess the exact contribution of this operation to the general effect of artificial pneumothorax, partly because it was normally undertaken within a few weeks of induction, that is, before the benefits of the artificial pneumothorax alone could be judged, and partly because the extent of the adhesions before operation was not noted. Thoracoscopy is best regarded as an integral part of the induction of the great majority of artificial pneumothoraces, enabling a lung free from adhesions to be obtained in about one-half, and varying degrees of satisfactory collapse to be obtained in a further quarter of all cases subjected to thoracoscopy.

Fluid complicating artificial pneumothorax.—It is unfortunate that nearly every author has a different classification for fluid, the reason being that there are five variable factors to be considered, namely, the quantity, the duration, the quality, the time of onset, and whether or not tubercle bacilli can be demonstrated. For statistical purposes, the following would seem to be the most satisfactory criteria:—

(1) Fluid should be considered to be present if it is sufficient to reach the top of the diaphragm.
(2) Transient effusions last less than three months, with or without aspiration.
(3) Persistent effusions last more than three months.
(4) An empyema consists of an opaque purulent tuberculous effusion in which tubercle bacilli are not necessarily demonstrated.

According to Trail (1932) and Clarke (1940) artificial pneumothorax alone gave rise to significant amounts of fluid in 50 to 60 per cent. before discharge from sanatorium. Following thoracoscopy, the series of Brock (1938), Laird (1939), Edwards and Lynn (1939), Edwards *et al.* (1944), Watt (1947), and Wollaston (1947), showed that it developed in approximately 45

per cent., being transient in 18 per cent., persistent in 20 per cent., and purulent in 7 per cent.

RESULTS OF TREATMENT

Sputum conversion.—Trail and Stockman (1932) and Clarke and Erskine (1940), treating patients before the advent of thoracoscopy, obtained 66 per cent. and 34 per cent. conversion respectively. Edwards *et al.* (1944), Laird (1945), Watt (1947), and Wollaston (1947) obtained an average of 82 per cent. conversion following thoracoscopy; Simmonds (1941), in a study of cavitating tuberculosis, obtained a conversion rate of 52 per cent. From these series it is apparent that with satisfactory collapse and cavity closure, with or without thoracoscopy, the figure for conversion approaches 90 per cent., and dwindles to the region of 20 per cent. for failed artificial pneumothorax treated by rest alone. The over-all figure for sputum conversion in any series is of great importance, both to the patients and the health authorities concerned (Livingstone, 1949), but it should be remembered that the criteria for a negative sputum vary considerably from one series to the next, and that a persistently positive sputum may be due to a number of causes beyond the control of the pneumothorax, such as disease in the opposite lung and tracheo-bronchial lesions.

Cavity closure.—Clarke and Erskine (1940) obtained 39 per cent. closure in cases of pneumothorax without thoracoscopy. Wollaston (1947) and Simmonds (1941) obtained 82 per cent. and 68 per cent. closure respectively, following thoracoscopy. Further confirmation of these latter figures is required, as cavity closure is one of the most important, if not *the* most important, function of internal pneumolysis.

Five-year mortality rates.—Trail and Stockman (1932) reviewed results at Midhurst, dividing their cases into three groups according to severity, and using as controls those in which artificial pneumothorax was unobtainable; Bentley (1936) compared all cases undergoing artificial pneumothorax in the London County Council institutions during one year and compared them with all other such cases, using the Ministry of Health classification; Hartley, Wingfield and Burrows (1935) compared cases at Frimley in group B3 undergoing artificial pneumothorax with comparable controls; Edwards *et al.* (1944) compared cases having artificial pneumothorax with those in which it had been tried and failed at the Cheshire Joint Sanatorium. Bearing in mind the variations in presentation, it would seem from these figures that there is an increase in the survival rate at five years of roughly 15 per cent. in groups A and B1, of 30 per cent. in group B2, and of 25 per cent. in group B3. The figures in groups A and B1 are small and little reliance can be placed upon them. Patients in group B2, comprising the bulk of those upon whom artificial pneumothorax is attempted, have their five-year survival rate almost doubled, if they are considered suitable for such treatment and this can be successfully carried out. The majority of patients in group B3 have a poor prognosis with any

form of treatment, but again, should artificial pneumothorax be feasible, a considerable prolongation of life may be achieved.

CONCLUSION

The authors quoted in this article, in common with almost all others upon this subject, are enthusiastic about the results of artificial pneumothorax. It may well be asked why it is not attempted more often. It is clearly undesirable as a routine for all minimal lesions, since about one-half are likely to show no radiological progression without such treatment (Reisner and Downes, 1945); should such progression occur, then artificial pneumothorax may well be undertaken with advantage (Turner and Collins, 1936; Heller, 1947) with little risk of complications. In the more advanced groups many patients are ruled out because their disease is too acute or too extensive, or they are over fifty, an age beyond which pneumothorax is rarely satisfactory; for those in whom it is attempted, a balance must be struck between the undoubted over-all benefits, on the one hand, and the complications to which it may give rise, on the other. It has already been pointed out that empyema follows about 7 per cent. of thoracoscopies; its total incidence is probably not less than 10 per cent. Large pleural effusions and contracted lungs may produce considerable disability. Clarke and Erskine (1940) estimated that death was directly attributable to artificial pneumothorax in 2 per cent. of their cases. Artificial pneumothorax is an excellent form of treatment both for tuberculous cavitation and progressive infiltration, but individual experience alone will determine which patients are most likely to benefit from it, and which are most likely to develop complications.

References

Barclay, R. S. (1943): *Edinb. med. J.*, **50,** 554.
Bentley, F. J. (1936): *Med. Res. Coun. Spec. Rep. Ser.*, No. 215.
Brock, R. C. (1938): *Brompton Hosp. Rep.*, **7,** 81.
Clarke, B. R., and Erskine, S. L. W. (1940): *Quart. J. Med.*, **33,** 323.
Edwards, P. W., and Lynn, A. (1939): *Brit. med. J.*, **ii,** 897.
——, Penman, A. C., and Logan, J. (1944): *Ibid.*, **ii,** 270.
Hartley, P. H. S., *et al.* (1935): *Brompton Hosp. Rep.*, **4,** 1.
Heller, R. (1947): *Tubercle*, **28,** 49.
Laird, R. (1945): *Ibid.*, **26,** 149.
Livingstone, R. (1949): *Ibid.*, **30,** 79.
Macnalty, A. S. (1932): "Reports on Public Health and Medical Subjects", No. 64, Ministry of Health.
Registrar-General's Statistical Review (1939): H.M. Stationery Office.
Reisner, D., and Downes, J. (1945): *Amer. Rev. Tuberc.*, **51,** 393.
Simmonds, F. A. H. (1941): *Tubercle*, **22,** 183.
——, and Martin, W. J. (1948): *Amer. Rev. Tuberc.*, **58,** 537.
Stocks, P. (1944): *The Practitioner*, **153,** 1.
Tattersall, W. H. (1947): *Tubercle*, **28,** 85.
Thompson, B. C. (1943): *Brit. med. J.*, **ii,** 721.
Trail, R. R., and Stockman, G. D. (1932): *Quart. J. Med.*, **25,** 415.
Turner, G. C., and Collins, L. L. (1936): *Amer. Rev. Tuberc.*, **34,** 792.
Watt, J. (1947): *Tubercle*, **28,** 158.
Wollaston, F. L. (1947): *Lancet*, **ii,** 424.

ACUTE CHOLECYSTITIS

By GUY BLACKBURN, M.B.E., M.Chir., F.R.C.S.
Assistant Surgeon, Guy's Hospital.

Unanimity of opinion about the treatment of acute cholecystitis has not yet been attained. The trend on both sides of the Atlantic over the past twenty-five years has been towards earlier operation, and there are many now who favour immediate operation in place of the more conservative attitude that has prevailed so widely and for so long. Walton, in 1923, was the first British surgeon to carry out immediate operation, although earlier writers had mooted the question. He wrote:—

"It is a remarkable fact that, although surgeons are generally agreed that an acute appendicitis should be treated surgically, since it is impossible to determine the course the disease will take, there are still many who advocate that an acute cholecystitis should not be operated upon until the acute symptoms have abated. This is probably due to the fact that a large percentage of the cases will, if left, gradually quieten down, until the gall-bladder forms a round distinct tumour, to which the omentum is adherent. There seems, however, to be nothing to commend this plan of treatment . . . As with acute appendicitis, so here, it is impossible to determine which cases will quieten down and which will progress to gangrene and perforation".

PATHOGENESIS

All writers are emphatic in describing a high incidence of stones in these cases of acute cholecystitis, and my own small series of twenty-six cases, with stones in twenty-five, falls very closely into line. This raises the question of etiology, well illustrated in the table by J. H. Saint (1943) of Santa Barbara.

ACUTE OBSTRUCTION + ACUTE INFLAMMATION
↓
INCREASED INTRAVISCERAL TENSION
↓
INTERFERENCE WITH THE BLOOD SUPPLY
↓
(TENSION) GANGRENE
↓
PERFORATION
↓
PERITONITIS

That bacterial invasion is a secondary phenomenon is now fairly widely recognized, and the inability to grow any organisms in aerobic or anaerobic culture from the wall and contents of the gall-bladder from eight personal cases has borne this out. It is fair on these grounds to stress the resemblance between acute cholecystitis and acute intestinal obstruction rather than acute appendicitis.

Patey and Whitby, in 1932, showed that Rosenow's theory of intramural bacterial emboli as the cause of acute cholecystitis was certainly not the invariable cause, and that the liver in some cases might not be an efficient bacterial filter. Ascending infection from the duodenum, as they pointed out, is probably extremely rare, if it ever occurs, and the purely obstructive aspect of the problem is clearly the more important. As Mailer (1939) and others have shown, this is easily demonstrable in sections of acute cholecystitis, and spontaneous rupture (in the absence of trauma) with marked bleeding into the peritoneum is recorded in five instances in the literature. If Rosenow's theory were correct, it might reasonably be expected that penicillin would affect those cases with infection due to *Streptococcus fæcalis*. Streptomycin might similarly be effective if *B. coli* were the offender. These organisms are both bile-resistant, but the work of Zaslow, Counseller and Heilman (1947) from the Mayo Clinic, and Rammelkamp and Helm (1943), has shown that no antibiotic agent can be demonstrated in the bile in cases in which the cystic duct is obstructed, whereas large amounts are demonstrable in cases in which the cystic duct is patent and the antibiotic agent is normally excreted by the liver.

TREATMENT

The patient's age is a most important consideration, gangrene being more likely with advancing years, and early operation on this account more justifiable. Mortality, of course, rises after sixty, but this applies to any surgical procedure. That operation is far safer now than twenty years ago and less hazardous than expectant treatment depends upon a number of factors: (1) improved methods of infusion and transfusion of blood and other fluids, and a better understanding of the correction of dehydration; (2) chemotherapy and antibiotics primarily to control not preoperative infection but postoperative morbidity, particularly above the diaphragm; (3) advances in anæsthesia, with curare as perhaps the greatest stride, and the relegation of chloroform and spinal anæsthesia to the place where they rightly belong; (4) controlled vitamin K therapy in jaundiced patients; (5) fibrin foam, gelfoam, oxycel and the like, to control liver oozing.

These are but some of the aids, and perhaps most important of all is a more widespread awareness that gall-stones need treatment to avoid complications like acute cholecystitis, and a waning in popularity of the proud boast of some physicians that gall-stones are often "silent". This emanated, I believe, from the post-mortem room, and it is too often forgotten that they have been posthumously dubbed silent only when their possessors were no longer able to voice an opinion. That the average middle-aged woman puts up with a number of things in silence is too obvious to require reiteration; dyspepsia is often one of them.

An interesting fact in relation to *early operation* has been pointed out by

Wallace and Allen (1941) in particular: namely, that gangrene occurred before the fourth day in only 10 of 415 cases, and perforation not at all. This would seem to be an argument in favour of surgical intervention before this date, but the first day of the disease is often very difficult to determine. Wallace and Allen showed that in 25 per cent. of their cases the first attack of acute pain was the onset of acute cholecystitis. In the remaining 75 per cent. previous attacks of pain had occurred. Pain, by itself, is therefore not conclusive, and exhaustion of the muscular wall of the gall-bladder and cessation of colic may be misleading, as the patient feels better while gangrene is supervening. A parallel picture may be seen in perforation of the appendix.

Graham (1944) has stated that the mortality is 2 to 3 per cent. if cholecystectomy is done after two attacks, 8 to 9 per cent. after three or more, 10 to 12 per cent. in the presence of jaundice, and 50 per cent. with pancreatitis. These figures, of course, favour operation early in the history of the disease, and the type of operation is important.

Choice of operation.—Barksdale and Johnston (1948), of Jackson, Mississippi, report the result of a questionnaire sent to members of the Southern Surgical Association:—

(1) In acute cholecystitis do you favour early or delayed operation? 101 answered early, 38 delayed, and 10 were non-committal.
(2) Is cholecystectomy or cholecystostomy your procedure of choice? The overwhelming majority were in favour of cholecystectomy.
(3) Do you advise concomitant choledochostomy? Only when definitely indicated. (Allen quotes a figure of less than 10 per cent.)
(4) Do you recognize a critical period in which surgery seems contraindicated? Most surgeons did not, but Allen quoted a mortality highest between the fourth and twelfth days.

My own answers to those questions would have been similar, reserving cholecystostomy for patients too ill for cholecystectomy, and particularly those with jaundice thought to be due to stones in the common duct. Subsequent cholecystectomy with choledocholithotomy is less hazardous then than at the primary operation. So far, however, in twenty-six consecutive personal cases, cholecystectomy has always been possible, with exploration of the common duct on three occasions. The Thorek or Martin modification of the operation has not been employed, but dissection from the fundus downwards has often been helpful. Apart from wound dehiscence, requiring re-suture, in one patient with a perforated gall-bladder eight days after cholecystectomy, convalescence was relatively uneventful in this series of cases and there were no deaths.

Marshall and Phillips's (1948) series of 74 cases from the Lahey Clinic with 9 perforations and 1 death is a fair example of what can and should be achieved to-day. 69 of these had stones and cholecystectomy was possible in every case but one, in which a preliminary cholecystostomy was performed. They end by quoting Heyd: "The indication is to operate carefully with due celerity, relieve the mechanical obstruction and provide drainage. Teachers of surgery who lend their prestige and

give support to a policy of waiting provide authority for timid surgeons, inexperienced operators and procrastinating practitioners".

High mortality in some series in early cases was attributed by Eliason and Stevens (1944) to the inexperience of the surgeon, anæsthetist and assistant, with perhaps a "pupil nurse as suture helper, likewise green and frightened". With this may be linked a reference to the paramount importance of identification of structures in relation to the common duct. Without meticulous care in this respect there is a risk of injuring the common duct, an accident that can and does happen in removing the gall-bladder. That one famous surgeon in the States could have had an opportunity of repairing it more than 200 times is, however, no reflection on cholecystectomy for acute cholecystitis, nor is it a challenge for us to provide a peer in this country. The vast majority of these accidents, in fact, happen in a pool of blood in cholecystectomy for cholelithiasis without any acute inflammation. The surgeon alone is to blame.

CONCLUSION

Twenty-six cases such as these is too small a series to permit of any conclusions, but an impression alone may be allowed. As a student I was always taught to observe acute cholecystitis and hope the worst would not occur. I now prefer to do otherwise and assess the danger of immediate operation as far less than that of expectant treatment.

References

Bardsdale, J. W., and Johnston, J. H. (1948): *Ann. Surg.*, **127,** 816.
Eliason, E. L., and Stevens, L. W. (1944): *Surg. Gynec. Obstet.*, **78,** 98.
Graham, H. T. (1944): *Ibid.*, **78,** 98.
Mailer, R. (1939): *Brit. J. Surg.*, **27,** 91.
Marshall, S. F., and Phillips, E. S. (1948): *Surg. Clin. N. Amer.*, **28,** 633.
Patey, D. H., and Whitby, L. E. H. (1932): *Brit. J. Surg.*, **20,** 580.
Rammelkamp, C. H., and Helm, J. D. (1943): *Proc. Soc. exp. Biol. N.Y.*, **54,** 31.
Saint, J. H. (1943): *Surg. Gynec. Obstet.*, **77,** 250.
Wallace, R. H., and Allen, A. W. (1941): *Arch. Surg.*, **43,** 762.
Walton, A. J. (1923): "Gall-Stones and Their Complications", London.
Zaslow, J., Counseller, J. S., and Heilman, F. R. (1947): *Surg. Gynec. Obstet.*, **84,** 16.

UNIVERSITY OF MICHIGAN LIBRARIES

OBSERVATIONS ON THE TOXICITY OF DDT

By ARWYN ROBERTS, M.D.

As soon as DDT was found to be a good insecticide, much research work was done to gauge its toxicity. Since it was first used, many papers have been published, but these disagree profoundly with each other as to its toxic effects. On perusing these papers, one is inclined to agree with Remington (1948) that DDT is the most publicized, most misrepresented and least understood of insecticides. A recent paper by Biskind (1949) of New York presents evidence that in America a prevalent symptom-complex which was thought to be of virus origin is, in reality, due to DDT poisoning. Plichet (1949) has recently described a gastro-enteric syndrome occurring in France, similar to that of Biskind and which, by a process of exclusion, he ascribes to the indiscriminate use of high concentrations of DDT.

Thousands of tests have been performed and hundreds of reports and papers written. What conclusions can be reached from their analysis?—what help on the problem can be given to the medical practitioner? The toxicity of DDT can certainly be under-estimated and can most certainly be over-stressed. It is fairly certain that differences in clinical manifestations depend not only upon concentrations and solvents but upon irregularity of absorption. What is the evidence?

PHARMACOLOGY OF DDT

DDT (dichlorodiphenyl trichlorethane) belongs to the group of chlorinated hydrocarbons and resembles them in some of its effects, especially on the mammalian heart. It is a fine powder, insoluble in water, rather inert chemically and very stable, and is used as the powder alone or dissolved in organic solvents. Its fate in the body is not well understood, and on ingestion it is excreted in the urine partly unchanged and partly as dichlordiphenyl acetate, which seems to be its only metabolite (Judah, 1949). When sub-toxic doses are taken over a long period, urine analysis can give valuable aid before early symptoms of toxicity appear. Dichlordiphenyl acetate is relatively non-toxic, and there is no conclusive evidence that DDT itself is the toxic agent in mammals. Further research will have to be carried out to elucidate the problem of its metabolism and the nature of the toxic agent.

SYMPTOMS OF TOXICITY

Small doses by mouth can cause nausea, vomiting, anxiety states, muscle stiffness and sore throats, whilst large doses cause anorexia, tremors, convulsions, with paralysis and death. The main symptoms correspond to those

produced by the ablation of the cerebellum and cortex; the myocardium is sensitized to fibrillation; tetany is produced but the part played by calcium metabolism is debatable; central necrosis of the liver may be found in the survivors of an acute episode.

Before DDT was introduced to Britain, extensive tests were carried out on it in Switzerland, where it was made. It was found that when animals were exposed to DDT in various strengths, the solvent, especially kerosene, played a major part in producing toxic changes. Chronic application of dry powder caused no changes in animals, and the sprinkling of 5 per cent. powders on the clothing and scalp of human beings had no adverse effect. Volunteers wore DDT-impregnated underwear for twenty days without general or local effects. All the hazards associated with the widespread use of DDT in the armed Forces were ascertained by hundreds of tests, in this country and in America, in 1943. Cameron and Burgess (1945) carried out extensive tests and came to the conclusion that only gross carelessness would be likely to lead to serious features and, provided a maximal concentration of 0.5 per cent. DDT be insisted upon for sprays, there would be no reason to anticipate any danger to man. These workers stressed that care should be taken in handling DDT in oily solvents and in highly concentrated sprays, and that food should not be contaminated. In America, Draize and Woodward (1944), amongst others, investigated DDT and found that in powder form it was not dangerous, but that if dissolved in fatty oils, it was.

The allied military authorities were satisfied with the tests, and DDT in suitable concentrations and solvents was extensively used in all theatres of war without untoward results. Minor irritation and slight toxic symptoms were reported from time to time but, considering the large-scale application of this insecticide under diverse conditions, the results show how safe DDT can be when properly used.

It seems that aerosols are less dangerous than had been thought; Stammers and Whitfield (1947), working at the Royal Naval School of Tropical Hygiene at Colombo, exposed volunteers to 5 per cent. DDT in kerosene aerosols for days, without ill-effects.

DDT POISONING

In acute poisoning, discontinuation of contact with DDT results in complete recovery, and even when liver damage has developed, a fatal issue is not necessarily inevitable. The *Manufacturing Chemist* (1949) quotes a case in which native dockers in Durban drank mugsful of DDT in kerosene, thinking it to be some form of alcoholic drink. After a few hours of severe illness, all but one were able to work the next day!

The main danger from DDT is from its ingestion. Food, especially garden produce, can become extensively contaminated by sprays. DDT powder can be confused with culinary powders, and toxic doses can be transferred to food from contaminated hands. Another serious problem is

UNIVERSITY OF MICHIGAN LIBRARIES

the spraying of such animals as cows and goats with excessively strong solutions, which are either absorbed through the skin or licked off. Telford and Guthrie (1945) found that DDT or its decomposition products appeared in toxic concentrations in the milk of sprayed mammals. An important public health problem arises here. Will the drinking of milk contaminated with small percentages of DDT from sprayed cows lead to cumulative poisoning, if drunk by adults or children for long enough periods? This is an important matter, and careful investigations should be made to assess the dangers. This is where the Medical Officer of Health and the observant practitioner can help each other. Is the neurological syndrome described in America due to cumulative poisoning which may take months, or even years, to manifest itself?

Acute poisoning with DDT is usually due to carelessness, uncleanliness, and poor supervision in experimental laboratories and factories. In the home, DDT in small concentrations, carefully applied, safely stored, and kept away from food, is quite safe. Hands contaminated with it should be washed, and it is a wise precaution to wash fruit and vegetables after its use in the garden. It should be remembered that a fly, after contact with DDT, does not die at once but flies about until it drops, helpless, maybe into food. After and during the use of DDT, food should be covered, for a dead or dying fly can be as dangerous a source of contamination as a live one.

CONCLUSION

It may be concluded that DDT used in the home as an insecticide is quite safe provided it is used with care and common sense. The question of long-term poisoning from contaminated milk is, however, a problem which demands further investigation.

References

Biskind, M. G. (1949): *Amer. J. digest. Dis.*, **16**, 79.
Cameron, G. R., and Burgess, F. (1945): *Brit. med. J.*, **i**, 866.
Draize, J. H., *et al.* (1944): *J. Pharmacol.*, **82**, 159.
Judah, J. D. (1949): *Brit. J. Pharmacol.*, **4**, 120.
Manufacturing Chemist (1949): **20**, 473.
Plichet, A. (1949): *Pr. méd.*, **57**, 1121.
Remington, J. P. (1948): "Practice of Pharmacology", 9th edition, London, p. 1235.
Stammers, F. M. G., and Whitfield, F. G. S. (1947): *Bull. entomol. Res.*, 38, 1.
Telford, H. S., and Guthrie, J. E. (1945): *Science*, **102**, 647.
Woodward, G., *et al.* (1944): *J. Pharmacol.*, **82**, 152.

THE MECHANISM OF SLEEP

By C. G. LEAROYD, M.R.C.S., L.R.C.P.

Most people spend a third of their lives asleep and some of them find it the most pleasant third. Many theories have been propounded about the mechanism of sleep, and Gillespie, in reviewing them, inclined to the view that it is a tidal and active inhibitionary movement spreading from the basal ganglia. Tumours in this region are sometimes associated with an active insomnia, going on to lasting somnolence; hypnotic drugs are concentrated almost entirely in the basal ganglia and almost not at all in the cortex (at least in animals); that is where they are found and presumably that is where they act; here is the meeting place of the various nervous systems, the part of the mind where passions and haggling, native prejudices and shrewdness contend that business may be done—in market hours.

"Hence there is a probability that the rhythmic diminution in the activity of the vital vegetative centres which occurs each twenty-four hours tends to produce a local inhibiting process which will irradiate over the rest of the central nervous system in suitable—i.e. non-excited—conditions such as are furnished by rest in darkness and quiet".

This article is going to suggest the determined and purposive manner of this spreading inhibition and it is written from the naturalist's or functional angle. That function plays its commonsense part in sleep is shown by the facts that the only signs of increased physiological activity are found in the greater tonus of the sphincters of the iris, bladder and rectum, in the sustained activity of the orbicularis oculi, probably the masseter, and often the infant's flexors, and in the increase of perspiration. Blood pressure and temperature fall, basal metabolism is lowered (but hardly at all if sleep is in daylight), respiration and peristalsis slow, but the common sense of function demands doubled guards at the gates and night duties elsewhere.

In writing about a nebulous subject like sleep it behoves the writer to be clear, lest he turn mist into fog. It is even legitimate to be didactic, and in this he has the example of a master. In his autobiography Freud wrote: "I proposed the division of the mental personality into an Ego, a Super-ego, and an Id". In fact this is an arbitrary division of the almost indefinable "mental personality" by a man with a vast experience of peculiar people. Yet that piece of didacticism has been useful in clarifying hazy processes, it has been the verbal point of departure for many brave voyagings, and it is nice to notice in those who use this supposititious trinity the pleasing human trait of personifying abstracts, which gave the classics their gods and us our John Bull and Uncle Sam. There are dozens of other ways in which the idea of mental controls, forces or levels might have been expressed in words; conceivably there may be better ways; for instance, is the sexually neuter word "Id" a happy one for the level, control or force which it is supposed to represent? Still, the psychologists have found the nomenclature useful and I intend here to follow in the steps of a master and be didactic,

UNIVERSITY OF MICHIGAN LIBRARIES

even assertive, in the matter of sleep, and in particular in the mode of its coming and going.

PRECONDITIONING FOR SLEEP

The animal man is kept alert to his surroundings by some dozen different senses. Pflüger's famous boy with one ear and one eye available as a means of communication with the outside world, and having no common sensation, fell asleep as soon as these portals were closed. When the senses fade under a narcotic they do so in a definite order:—

"Alcohol successively weakens and suspends the hierarchy of functions of the brain, and therefore of the mind, in order from above downwards; that is to say, in the inverse order of their development in the individual and in the race . . . it will progressively affect a similar paralysis of other nerve paths in the descending order of functional dignity; and thus it facilitates escape from reality and from feelings of weariness, encouraging day-dreaming, wish-fulfilment and a general regression towards the earlier and more primitive levels of childhood and infancy".

The narcotic, alcohol, in short, hastens rather dramatically the ordinary preconditioning for sleep. Here are three points which I want to emphasize because they are essential to the understanding of the sleep regress:—

(1) Each sense is dealt with in order and alone. Is it strange that the protecting senses, each one of which must have taken countless centuries of striving and obsession to forge, should in their brief, nightly recapitulation be dealt with each in turn?

(2) When a sense is being dealt with it obsesses the remnants of consciousness, the organism's neural attention.

(3) Having occupied the whole stage, it is faded out—"patterned" is the word I am going to use—in such a way that stimuli that suggest danger can rouse it; then, and not till then, is it allowed to sleep, and the next sense in order is dealt with in the same way.

That account of the action of alcohol will do well enough as indicating the state of mind before sleep comes. There are just two comments I should like to make about this preparatory period:—

(1) One of the first senses to go has no specific name; it is a social sense, which is aware of the presence of others, that upholds the part we are supposed to play and the personality we would impose, call it the "façade sense". Even as we undress it captures our consciousness, then fades on condition that certain specific stimuli shall rouse it—a night 'phone call, for instance. It is the surrender of the little bit of individuality that man has been able to acquire.

(2) Gillespie writes in his book, "Sleep": "Another characteristic of mental processes during sleep is the predominant rôle of visual images in the dream in comparison with the much greater part played by verbal images in waking life". The vast majority of people would not be struck by this because visual images are their usual currency of thought. Verbal images are rare with them, if by that term are meant seen words or numerals. Heard words, of course, are the next most common form of thinking after visual images. Only scholarly, bookish, and academically clever people—

like Gillespie—or those who are professionally occupied with the written word, think to any extent in verbal images. Naturally they and other complex forms of thought like concept and abstract thinking fade in the stages preliminary to sleep; fade after a brief display.

THE SENSE OF SIGHT

The visual sense with its long protective range in daylight becomes of little value in darkness and even in bright moonlight has a lesser range than hearing. The complete regression of the organism in sleep is impossible in light: "an observation that supports this view is the lesser metabolic change that occurs in sleep in darkness compared with sleep in light" and "it is an interesting fact that sleep in darkness diminishes the total output of all urinary constituents more than sleep in the light". The eyes in sleep are turned upwards and are slightly divergent; obviously in order to have a wider angle for the warning of light in a lying curled position. The pupils are narrowed, which represents a compromise between the demands for darkness and for safety; "we must have the curtains drawn a bit, my dear, lest dawn come without our knowing"; even so does the hibernating butterfly seek half-lights.

Even as a boy I noticed that one cannot day-dream and observe at the same time; images from reality displace imaginary images and *vice versa*. What is more, after a spell of imagining you observe better and after a spell of observation your imaginary characters and scenes come flooding back with increased vividness. When the eyes close and in the first stages of sleep the mind gradually gives up its daytime thoughts, to which all the senses contributed: sight, hearing, taste ("That really was an excellent piece of gorgonzola"), touch, smell, labyrinthine ("I must have the springs of the armchair seen to"), and so on, then it gradually settles down to giving its whole attention to one sense, and the first sense is the visual. As the eyes close and are shut off from functioning, a vivid imagery claims the attention. Scenes flash on and off, come human forms, some known, some strange, some changing as we watch; close-ups like Cheshire cats, all heads and looking weird, coloured at first, then black and white, then grey.

All dreams occur during the early stages of sleep or the late stages of waking, which may occur a dozen times a night; that is to say, while the visual and auditory senses are being dulled or wakened. Only in the lightest forms of sleep do the figures talk or are scenes synchronous with sound. As the light dream gets deeper the figures become less spontaneous in their utterances: the visual is being separated from the auditory, the whole of the organism's attention is being concentrated on one sense, which, I repeat, is the very essence of sleep, and incidentally of hypnotism.

Anyone who is integrated enough to feel his childhood will recall the awful feeling sometimes on waking, especially on being suddenly wakened from a daylight sleep. The young animal has been brought from a state of obsession by one sense to an environment that demands many, and the

UNIVERSITY OF MICHIGAN LIBRARIES

awful feeling is a failure of quick adaptation. "Nocturnal paresis" in adults is due to the same cause. The precedence of sight over hearing can be shown in regressions other than sleep. A doctor who as a girl on several occasions half fainted in church and was led out, told me that her sight went a blank grey, but the sounds of her feet on the aisle came with awful clearness. Anyone who has been knocked out boxing will remember how vision is reduced to revolving circles, which, of course, is patterning, but one hears the sound of one's body hitting the boards with engrossing clarity.

It is during the visual stage of sleep that the great majority of dreams occur; all dreams that are coherent enough to be recordable and therefore able to be memorized except in a merely impressionist way must come from the visual or auditory layers. This is no place for a dissertation on dreams, but it is obvious that basal desires and racial longings have an opportunity, possibly their only opportunity, of expressing themselves in dreams by symbolism and masquerade. A man unburdening his soul over a quart in the bar-parlour is doing only in a lesser degree and with a little more guile what he will be doing in his dreams in an hour's time. Night terrors in children come from this stage; they are often caused by acidosis, that is to say, a ravening need prevents the visual being patterned by fabricating a silent ghost film. Nightmares also are panics from battles elsewhere—as the world knows. Their function is to prevent any deeper sleep until the battle's over. What awful things might happen if one vomited in sleep!

As the organism becomes engrossed with the visual the images become silent and in their silence strange. Gradually they lose colour, lose outline, and finally there is a slowly moving pattern of different greys. The whole point of the pattern is this: any alteration in the pattern will mean either that light is coming in or that there is a disturbance in the lower layers, and if either happens the patterning will go into reverse and images will come again. The point of the grey is that this is the best background for showing up coloured light, and all light coming through eyelids is reddish.

The visual apparatus is now asleep—in the same way as an unexposed film in a camera is asleep.

THE SENSE OF HEARING

The auditory sense is the chief guardian of the sleeper from dangers without. Let us recall how the ears deal with sound in a world where sound is in chaos. A man travelling in a train at sixty miles per hour is assailed by a thousand noises; he turns them neatly into ter-um-titi ter-um-titi ter-um, ter-um-titi . . .; then and then only can he disregard them. If some minatory noise or some noise that has especial importance to him, say, the sound of the ticket collector if he has no ticket, comes and breaks the pattern of noise, he is alert. When the bombing aeroplane is heard it breaks the pattern of one's own near noises, so that one hears one's breathing and heart beat. The most impressive instances, of course, come from the natural world: an angler standing in a stream with a thousand voices which he harmonizes

very pleasantly and forgets, has the pattern broken by the sound of a small trout jumping. Some noises have been evolved to break auditory patterns—the dog's bark, the child's cry. The auditory pattern is also broken by the cessation of one of the orchestra: when the ship's engines stop the sleeping seamen wake. The patterning of one's own near noises, the rustle of bed clothes, the heart beat and breathing, is often broken in the night by extra-systoles and rhonchi. The soporific effect of music is due to its being patterned noise with a guarantee of safety. When we hear of people sleeping in heavy gunfire we admire the miracles that the patterning of noise can perform—and think of jazz.

Just as you cannot be conscious of real and imaginary images at the same time, so it is with sounds. The outside noises having been patterned in such a way that the pattern will be broken by, say, a sound in the bedroom, a siren five miles away, a furtive latch-key sound; the stage of the mind is flooded by a host of phantom voices. Many people who doze off while reading will know how after the eyes are closed the imagery which the words evoked fades, but the words go on and on, not meaning anything, but true to trend and style—the majestic organ-voice of *The Times* leader, the insistent, short-sentenced nagging of the *Daily Energetic*. This has been called "doze-jabber"; in fact it is the auditory caught in the act of patterning.

When a noise breaks the auditory pattern, and indeed when any other pattern is broken, the whole mechanism of sleep is set in reverse; the visual is aroused and often incorporates the noise into what appears to be a long dream but may take place in a few seconds.

"A dreamer heard the executioner's bell toll, saw himself given religious rites, being walked a long distance through subterranean corridors, and finally being led to the scaffolding, where the hangman's noose was painstakingly adjusted around his neck. He waked to find that his long and anguishing experience had started when his alarm clock began to ring—less than thirty seconds before".

It is because of its extraordinary adaptability, and its engrossing quality, that the mechanism of sleep is not apparent to all. Purely auditory dreams are common, but being like Chinese plays all talk and no action they are not so often remembered or recounted. The patterning of phantom voices and sounds is the last coherently recordable stage of dreaming.

The auditory apparatus in sleep is the most efficient and selective burglar-alarm in existence, but it is sometimes sprung by a cat or a policeman.

THE SENSE OF SMELL

The olfactory sense in man is semi-atrophic, whereas in dogs it gives rise to the logic of their thought and, almost certainly, olfactory dreams are as dramatic to them as visual ones are to us. Our sense of smell has the child's trick of quick noticing and quick forgetting: we smell the roses only when first we come to Paradise, which is sad, but the stench of the slum assails only the stranger, which is not so sad. It is doubtful whether the olfactory layer of sleep gives recordable dreams. A disturbance of the olfactory pattern can certainly set the mechanism of sleep in reverse and be incorporated in the

UNIVERSITY OF MICHIGAN LIBRARIES

auditory and visual reawakening, as is shown by people being woken up by the smell of burning furniture or the aroma of kippers.

Although our olfactory sense is semi-atrophic, and is therefore satisfied with a simple childish patterning of smells, it does not follow that in the regression of sleep, when in its turn it claims all attention before being put to bed, it will be of little note now; it does not follow that its complaints will not be listened to, that its old importance will not be recognized. This is the level of sleep where nocturnal asthma starts. In my view asthma, although not always caused by a respiratory invader, is always the body's response to a respiratory invader, real or imagined. During our early millennia, when we were so intimate with the earth, it was by far and away the most common invader, and the shallow breathing in and violent breathing out through narrowed tubes was the obvious way to get rid of it; tobacco ash on the sleeve calls for the same action, exteriorized a bit. When the organism in the process of sleep is wholly concerned with the olfactory sense, with hearing its complaints, patterning it and putting it to bed, it may refuse to pattern in the presence of a respiratory invader or an imagined one; for the sense of smell is the guardian of respiration, as it is the consultant of taste.

I was for some years on a passenger ship that crossed the equator every month. As we got into the humid area I nearly always had patients with asthma from a certain group of cabins. Some of them had had asthma or one of its shallower variants before, others had not. The pillows in these cabins were stuffed with feathers and smelt. Obviously the feathers were infected with a mould which spored or whose spores were inhaled in greater quantity in humid weather. But the smell of the feathers did not keep them awake; their modern, superficial olfactory sense patterned that, but they woke from sleep with asthma. Manifestly, from the olfactory level of sleep.

THE LABYRINTHINE SENSE

I am not erudite enough to know whether this should come before or after the olfactory. They are both on the edge of recordable dreamland. In modern landsmen this sense too is atrophic; they wish it wasn't when they get to sea, for it is the inability to pattern movement that causes seasickness. The ease with which this ability is acquired is very suggestive of its old importance—probably in arboreal man.

When I was at sea I found sleep came very quickly if I let my mind dwell on the rhythm of the ship's movement. If the rhythm changed in the night, say, from the roll of a beam sea to the figure-of-eight movement from a sea on the quarter, I would half wake, adjust the rhythm, and go to sleep again. At church service I sometimes used to watch the sailors adjusting in their swaying the tune, say, of "For those in peril on the sea" with any type of predictable or unpredictable movement of the ship; a miracle of unconscious adaptation.

In infants this is probably the highest organized sense, and the rocking of the cot induces patterning and sleep. Older children who have the bad habit of rocking or swaying in bed or of rhythmical head-beating are going back to an infantile mode of solace and sleep. The rhythmical swaying of old people, poor captive animals, and the joy of swings are relevant here.

Although it is impossible to be sure of anything in this unchartable level

I am convinced that it is here that some enuresis takes place. It would take too much space to display all my evidence, but as a child, more than half a century ago, I remember that my one lapse from the chastity of nocturnal dryness was accompanied by a feeling like sliding down a hill—thrilling; it is significant how tenacious are the memories of one's social enormities. The small child's last failures of daylight continence are in response to the emotions of wonder and fear combined; the switchback and stunting aeroplane can on occasion defeat the adult. Possibly an arboreal habit of jettisoning cargo in a storm may show itself as enuresis at this level—in spite of the doubly sealed sphincter. Treatment? Swings and switchbacks t.d.s., of course.

THE SENSE OF TASTE

It is said that one never tastes in dreams; it would be truer to say that taste-dreams are a long way below the verbalizing visual and auditory layers of sleep. Like the olfactory, the gustatory depends upon movement, but whereas the olfactory has its stream passed over it by the mechanism of respiration, the gustatory has to use the surrounding muscles; food to be truly tasted must be on the wing. The swallowing efforts in one stage of anæsthesia indicate that the gustatory level has been reached.

THE THERMAL SENSE

When animals first had the presumption to raise their temperatures above that of the earth, they played with fire; they gained independence at the cost of hazard. For millennia untold the question of upholding his thermality must have been of terrifying importance to man, especially at nightfall. That is why the thermal sense has an overriding precedence among the senses in sleep; the very beginning of sleep, the dance and eclipse of the visual, is prohibited if man's sovereign temperature is threatened, even by cold toes. Heat below this or above it must be equalized. That, of course, is the purpose of the increased sweat activity in sleep. Increased sweat when it is allowed to evaporate causes a loss of heat, but when it is not allowed to evaporate by coverings of hair or family huddling it gives a blanket of humidity. Night sweats in tuberculosis or wet packs may be attended by clammy discomfort, but not by coldness. The extraordinary mental peace one gets from a hot bath is due to the mind being relieved from one of its oldest fears. The lower temperatures of hibernating bats and sleeping men may be regarded as an abatement of impudence at times when bluff might be called. If the thermal sense has not used his veto voice during the earlier stages of sleep he is heard and patterned with his twin sister "touch".

THE SENSE OF TOUCH

Thermality is the dominant twin and must be appeased first, but touch is more charactered. This is the level of sleep where the old skin complains, and its whining is called senile pruritus, where clothes are thrown off or over

UNIVERSITY OF MICHIGAN LIBRARIES

the head, this is where the acne pricks and the scabies mite seems to burrow. Kenneth Mellanby has shown that they do not; they are probably as anxious to rest as their host, his falling temperature must be to them as the setting of the sun.

It is to induce regression to this stage that the Teddy Bear is hugged, and, oh! how much wiser is the child than the fool who advises one to count the sheep of imagery to get the sleep of contentment; to stay up in the anxious crow's-nest of the visual. This is the farewell stage to the outer world when the skin takes cognizance of its immediate surroundings. To this stage the conjugal clasp and for ninety-nine per cent. of man's existence here on earth the family huddle, both of which thriftily lessen the overheads for heat and safety, invite the sleeper.

Now as to the therm-touch patterning with its vast and diverse area—like the Empire, some parts hot, some cold, some temperate, some humid, some parts pressed on and not minding, others impatient of the slightest touch, some highly skilled in daylight now in dark are finger-tips near dead, foretasting that continuum men call death—are not these matters for a monograph?

JOINT AND MUSCLE SENSES

The last main senses to claim the whole attention in regression are the muscle and joint senses. It has been shown experimentally on some poor wretched dogs that the flaccidity of muscles during absolute sleep is more than in waking rest or paresis. This is where the guardian muscles of a diseased joint go off watch, and the sudden pain of raw areas rubbing together wakes the sufferer from the very edge of absolute sleep and sends his mind back in a few seconds through all the stages of numbing which it may have taken half an hour to traverse. This is where the gouty joint declares itself: "Damn it, I'd just got off into a decent sleep . . .".

I was once camping with a man in New Zealand when he hurt his knee. In our tiny tent he tossed about all night (from which, of course, one has to subtract several spells of several hours spent unconsciously and therefore instantaneously). I sympathized, then expostulated, then cursed, but he didn't take the slightest notice, which at the time I was inclined to attribute to stubbornness. Next morning it struck me as amazing that a man should be capable of all that movement and yet sleep.

I have often seen this phenomenon since; it is the muscle and joint senses having their fling, protesting that it is not safe to go into immobility in this or that position; it is the "rough house" period of the anæsthetic, which comes so surprisingly after quiescence. The reason why it lasts so long is that it upsets the touch-thermal pattern, a foot out of bed, for instance, and starts the whole process over again. Apparently the thermal does not panic when it is roused in this way; there is a good deal of give and take between these last two groups of senses.

SLEEP CURVES

The depth of sleep which has been measured by the amount of noise that is

required to awaken and by other methods is found "in children to have two maxima of depth, one being reached in the first or second hour and the other, not so deep, in the seventh hour, deepening to the ninth, when it rapidly shallows till the child awakes". In adults there is only one maximum, usually early but variable. Apparently the child has more need of some primordial refreshment.

What happens in deep sleep is a matter of conjecture. We know that the autonomic systems which have, as it were, a Dominion's Office in the basal ganglia carry on with Whitehallian week-end energy, that the sphincters and other night workers keep special gate and guard, that infant flexors often clench—surely an old arboreal trick, this—that sweat increases with immobility, that meninges pale, and knee-jerks go, but little else. But if a road is marked "To York" and gets as far as Thirsk or Doncaster we should be sceptical indeed if we doubted if it went to York. In sleep we retrace the path by which we've come to our solemn, self-important maturity; we go back to youth, to childhood, to fœtal days with their aquarium life. In deepest sleep no doubt unseen, unheard, unfelt things are experienced, slow turnings towards some glimmer of light, the goodness of growth, shrinkings from the chemically strange. Words to express them are many million years away, yet such is the miracle of rhythm, diastole and systole, night and day, sleep and awareness, that a mind from being in this state can in half an hour be directing a practice or ordering a home.

THE APARTNESS OF THE SLEEPER

We have seen that every possible precaution is taken against natural disasters, but what about our friends? A sleeping person evokes almost a sense of sacredness in the watcher, akin to that which is evoked by a corpse. A man asleep in the club or railway carriage demands the tribute of tipped toes and hushed voice; sometimes he looks so grotesque that he rouses fear, especially in children. Sleeping women and children assume a deceptive innocency which rouses our protective instincts. I myself get quite a kick out of looking at hibernating animals, of which I have several in the house at the moment. After all this time no ordinary forgiving person would be indignant with Jael and Macbeth for being murderers, but to murder a man in his sleep!

EPILOGUE

Suddenly the writer's assertiveness leaves him. This article has no charts or statistics and every reader is a potentially hostile witness. Will they testify truly? Men have little conscience for veracity in immaterial matters, in dreams, in spiritualism, in experiences abroad. They try to make their tales credible, and sometimes creditable, whereas if they are authentic they must be bizarre and humiliating.

He consoles himself with the conviction that his song—or parts of it—can be set to the cosmic tune.

UNIVERSITY OF MICHIGAN LIBRARIES

CURRENT THERAPEUTICS

XXVII.—MUSCLE RELAXANTS

By WILLIAM W. MUSHIN, M.B., B.S., F.F.A.R.C.S., D.A.

Director, Department of Anæsthetics, Welsh National School of Medicine, Cardiff.

"Muscle relaxants" are drugs which cause paralysis or "relaxation" of the voluntary muscles, without affecting consciousness or sensation. The best known and oldest example of a relaxant is curare, the South American arrow-head poison, the drug which acquired such a horrific reputation that special legislation, still in force to-day, was enacted to prevent its injection into conscious animals.

The story of curare goes back to the days of Sir Walter Raleigh who provided actual samples. Pharmacological studies initiated by Claude Bernard established that the site of action of the drug was at the neuromuscular junction. For over 100 years curare has served the pharmacologist, immobilizing animals without loss of sensation or serious side-effects.

In the clinical field, Ranyard West stands out as an early and enthusiastic advocate in this country of the therapeutic use of curare. His comprehensive paper in 1935 pays tribute to French workers in the last century, who used curare to treat convulsive diseases like hydrophobia, tetanus, epilepsy and chorea. The variability and lack of standardization of the curare extracts available at the time were probably responsible for the unpredictable results which so confused investigators. A great step forward was the isolation of *d*-tubocurarine chloride by Harold King in 1935, and the pure alkaloid is nowadays readily available and universally employed.

The modern story of curare begins with its successful use by Bennett of Nebraska for "softening" the spasms of electro-convulsion therapy. He suggested to Griffiths of Montreal that curare might be useful to obtain relaxation in anæsthesia; it was—and Griffiths's report in 1943 was followed by a flood of others from anæsthetists all over the world.

SYNTHETIC CURARE-LIKE SUBSTANCES

During the war, when supplies of crude curare became short, the stimulus was great to find substitutes, natural or synthetic. Many substances were already known to have curare-like properties, but it was not until after the war had ended that more satisfactory synthetic preparations were produced. For a brief period "myanesin", not strictly a curare-like drug, was tried in anæsthesia, but enthusiasm for it evaporated for reasons given later. Within the last year "decamethonium iodide (C10)" and "flaxedil" have been put on the market. The latest newcomer is "metubine iodide".

d-Tubocurarine chloride, a pure crystalline alkaloid, is sold in ampoules usually containing 15 mg. dissolved in 1.5 ml. (i.e., a dilution of 10 mg. per

ml.). At least one American firm puts up the drug in ampoules containing 3 mg. per ml., so that the label on any ampoule should be read carefully before use. Eli Lilly & Co. have produced a derivative of curare called "metubine iodide" (dimethyl tubocurarine iodide) which, although identical in its effects, is some five to six times more potent than *d*-tubocurarine.

Decamethonium iodide, originally known as C10, is now marketed as "eulissin" and "syncurine". It is a synthetic substance with a powerful, curare-like effect. The exact site of its action seems to be different from curare, since the antagonist is not prostigmin, but another similar compound, hexamethonium bromide, called C6. An unfortunate side-effect of C6 is a marked lowering of blood pressure, and great caution should be exercised in its use. Weight for weight, decamethonium iodide is some five times more potent than *d*-tubocurarine.

Flaxedil is the trade name of the other synthetic substitute for *d*-tubocurarine. The effect of flaxedil is indistinguishable clinically from that of *d*-tubocurarine, except that the duration of the effect of an equivalent dose is slightly shorter. Prostigmin is an effective antidote. Flaxedil seems to be the best synthetic substitute for curare available, and has the not inconsiderable virtue of being made in this country at little cost.

MODE OF ACTION OF CURARE-LIKE DRUGS

Stimulation of a motor nerve causes a production of acetylcholine at the myoneural junction. This initiates the muscle contraction, either directly or by so altering local conditions as to allow certain ions, such as potassium, to act on the muscle fibre. The acetylcholine is normally quickly removed by hydrolysis by an enzyme, cholinesterase. Curare somehow prevents acetylcholine from reaching and causing contraction in the muscle fibre. Prostigmin, the antagonist to curare, is "anti-cholinesterase"; the destruction of acetylcholine is prevented, and acetylcholine accumulates to such an extent that the barrier set up by curare is overcome.

Following intravenous injection all the voluntary muscles are progressively paralysed. The muscles of the limbs are paralysed first and then the muscles of the abdominal wall. The intercostals then follow, whilst the diaphragm is the last to be put out of action. With sufficient dosage complete muscular paralysis of the whole body results, with, of course, cessation of respiration.

The transmission of impulses across the synapses between the pre- and post-ganglionic sympathetic fibres is also mediated by acetylcholine. A paralysis of this mechanism, too, is produced by curare-like drugs. This action may account for the marked bleeding which is so commonly seen at operations when curare has been administered. These drugs have no effect on sensation or consciousness, and an anæsthetic must be administered simultaneously or the worst imaginings of novelists (with whom arrow poison was once so popular) may well come true. No clearly demonstrable effect is produced on involuntary muscle, whether of gut, heart, or uterus,

UNIVERSITY OF MICHIGAN LIBRARIES

neither is there any upset of renal or hepatic function, so long as pulmonary ventilation and oxygenation of the blood are adequate. During curarization, histamine is liberated in the body, but what harmful effects can be laid at this door is not yet clear.

DANGERS OF CURARE-LIKE DRUGS

The great hazard of curarization is overdosage. Fortunately, there are few side-effects beyond muscle paralysis, and respiratory arrest due to curare need not be regarded with anxiety so long as adequate artificial respiration is maintained. How this is carried out is relatively unimportant, so long as it is efficient. These drugs should not be used unless the administrator possesses the ability and the means of carrying out efficient artificial respiration. Anæsthetists find it convenient and effective to use rhythmic compression of a bag, transferring its contents to the lungs of the patient. Prostigmin in adequate dosage is a powerful antidote to *d*-tubocurarine, metubine, and flaxedil, and the paralysis caused by these drugs may be reversed in a matter of minutes by its injection. The cardiac, glandular, and intestinal effects of prostigmin are neutralized by atropine; if the patient is not under the influence of his preoperative atropine, a further dose should be administered with the prostigmin. A suitable initial injection for a fully curarized healthy adult would be 2.5 mg. prostigmin given intravenously. This may be mixed with 1/100 grain (0.6 mg.) of atropine. These doses need to be reduced, and given in divided portions to the aged and the ill, as accidents have followed larger doses.

A second hazard (more theoretical than real, although instances are known) is insufficient general anæsthesia, the patient being partially or wholly conscious, but unable because of the paralysis to demonstrate this to anyone around him. Only sound experience of general anæsthesia can obviate such an unfortunate occurrence.

A third hazard lies in the return of the curarized flaccid patient to his bed without adequate supervision. Although lightly anæsthetized—maybe even conscious—his relaxed jaw and tongue make him analogous to the deeply anæsthetized patient after general anæsthesia. No patient who has received a relaxant should leave his anæsthetist unless it is clearly evident that all paralysis has disappeared. Vigorous breathing and active reflexes are the signals of safety.

Myanesin.—This synthetic substance is not an ammonium substitution compound like the true curariform drugs, but is a glycerol ether. Myanesin does not act on the myoneural junction; the spinal cord or even higher still in the central nervous system are probable sites. Insoluble in water it is put up in an organic solvent. When injected, muscular paralysis is produced, superficially resembling curarization. Respiration is strikingly unaffected. Prostigmin does not reverse the paralysis, although absence of an effective antagonist for myanesin is offset by the evanescence of its action. Two serious side-effects of myanesin have damped any enthusiasm for its use in

anæsthesia: hæmoglobinuria due to hæmolysis, and thrombophlebitis at the site of injection.

DOSAGE

Whichever drug is used, and before any general anæsthetic is administered, a test dose (about ¼ the proposed initial dose) should be given, followed by a pause. Marked drooping of the eyelids and slurring of speech will demonstrate that the patient is likely to react unduly. The patient with unsuspected mild myasthenia is not a rarity. A test dose enables this to be discovered before and not after he succumbs to what may otherwise be a safe dose of relaxant. The following table (table 1) is a rough guide to dosage for healthy adults: these doses must be reduced greatly in ill or old people.

TABLE 1

	Test dose	Initial dose	Subsequent doses
d-tubocurarine (10 mg. per ml.) ..	5 mg.	10–15 mg.	1–3 mg.
Flaxedil (40 mg. per ml.)	20 mg.	50–80 mg.	10–20 mg.
Myanesin (100 mg. per ml.)	100 mg.	0·5–1 g.	0·5 g.

CLINICAL USES OF RELAXANTS

Anæsthesia.—This is the prime field for these drugs. Light anæsthesia maintains unconsciousness. Immobility and suppression of skeletal reflexes are secured by the relaxant. Reflexes such as handling the viscera, stretching the perineal sphincter, or stimulating the tracheo-bronchial tract, which would otherwise need the deepest of general anæsthesia, are easily obtunded with a relaxant. The use of curare may be compared with local anæsthesia. In the latter the reflexes are broken on the sensory side: in the former they are broken on the motor side. The relaxants have no effect on sensation. Former theories that, say, abdominal operations performed under light anæsthesia, are likely to be followed by shock, must be reconsidered, for shock-free recovery is characteristic of the skilful combination of light general anæsthesia and relaxant. It does not matter greatly what form the general anæsthetic takes; it must, however, be light, if the benefits of curare are to be obtained. The deeper the general anæsthesia the less relaxant is needed. Each general anæsthetic has its own peculiarities when used with relaxant, which the anæsthetist gets to know with experience. For example, some caution is necessary with ether; this agent by itself gives good relaxation, and unless the ether is administered skilfully so that light anæsthesia is maintained, curare will seem unduly potent. On the other hand, when nitrous oxide and oxygen alone are administered, rather larger doses of relaxant are needed, and it may be that in this instance adequate relaxation for abdominal surgery becomes synchronous with respiratory arrest. Better results are obtained when the nitrous oxide is supplemented with a little thiopentone or, as has been described recently, with small doses of pethidine, intravenously. Short procedures like intubation of the trachea or

bronchus, the setting of a difficult fracture, dilatation of the anal sphincter, deep palpation of the abdomen, manipulation of a joint, all otherwise needing profound anæsthesia, may be performed with ease and speed by combining a general anæsthetic like thiopentone with a relaxant. At any desired moment, residual curarization may be reversed by prostigmin.

Electro-convulsion therapy.—The previous injection of a relaxant "softens" the convulsion to such an extent that restraint is unnecessary and fractures become a rarity. In addition, the strain on the heart and circulation is so reduced that old and feeble patients, formerly considered unsuitable, may be given treatment. In one method of administration the relaxant is injected very slowly with many pauses, until the patient is just unable to snap his fingers. The convulsion is then induced. In another method a small dose (0.3 g.) of thiopentone makes the patient unconscious. The relaxant is then injected in a dose depending upon the patient's body weight (e.g., for *d*-tubocurarine, about 2 mg. per stone [0.3 mg. per kg.] is given). The lungs are inflated with oxygen if cyanosis appears, and prostigmin is given at the end of the treatment.

Spastic and allied diseases.—Relaxants have been used with marked success to alleviate spasticity in a host of orthopædic and neuromuscular disorders. Examples are: muscle spasm following acute trauma and also that associated with certain orthopædic deformities and joint diseases; spasticity following spinal cord injury; degenerative disease of the central nervous system, disseminated sclerosis; post-encephalitic Parkinsonism; and early rheumatoid arthritis. Good results have also been reported in poliomyelitis; muscle spasm is greatly improved and pain therefrom relieved. When spastic gait is present, great improvement may occur and patients have been able to do things previously difficult or impossible. Children with congenital spastic disorders form another promising group for curare therapy. Improvement in these difficult little patients is often striking, and progress under physiotherapy accelerated. In all these cases no tolerance to curare develops, even when the drug is administered over long periods of time.

When treating spasticity, a prolonged mild effect is desired. This is obtained by using a preparation containing *d*-tubocurarine in oil ("tubarine oily"), or in beeswax and oil. Such injections may be given hypodermically or preferably intramuscularly. A recent introduction in this field of therapy is "myanesin elixir", a palatable preparation taken by mouth. One tablespoonful of this elixir contains 1 g. of myanesin. The administration of myanesin elixir is stated to produce striking results in spastic plegias following cerebral hæmorrhage, as well as in other motor neurone lesions. The absence of any effect on the respiratory muscles makes myanesin an attractive drug for the treatment of these conditions and the investigation of its use in this connexion deserves encouragement.

Tetanus.—The relaxants are effective methods of controlling the spasms of tetanus. With skilful dosage the spasms are damped sufficiently to remove

the danger of asphyxia, the pain, and the apprehension, while still allowing adequate spontaneous respiration. An ever-present possibility is a temporary overdose of relaxant and, as a safeguard, instruments for tracheal intubation and a mechanical respirator should be kept near at hand. Swallowing is often affected and stomach-tube feeding may have to be relied on. Here again, myanesin may be the better drug, for it gives adequate softening of the spasms with no interference with respiration.

CONCLUSION

The muscle relaxants are powerful drugs which produce partial to complete paralysis of the voluntary muscles. They have no effect on the vital organs of circulation, metabolism and excretion. Their only real danger is temporary paralysis of the respiratory muscles, easily countered by artificial respiration by those familiar with respiratory control. In the case of *d*-tubocurarine and flaxedil an immediate reversal of effect is obtained by an injection of prostigmin. The ever-present possibility of respiratory arrest and the need for maintaining light anæsthesia when no signs of anæsthesia can be elicited, must restrict the use of relaxants in anæsthesia to skilled anæsthetists familiar with the treatment of apnœa.

Electro-convulsion therapy may with the help of a relaxant be carried out without the need for restraint, and without the risk of fractures. Muscular spasm, whether due to tetanus, trauma or organic disease of the central nervous system, responds to suitably graded doses of these drugs.

Selected Bibliography

History and Pharmacology

McIntyre, A. R. (1947): "Curare. Its history, Natures and Clinical Use", Chicago.

West, R. (1935): "The Pharmacology and Therapeutics of Curare and its Constituents", *Proc. Roy. Soc. Med.*, **28**, 565.

Anæsthesia

Gray, T. C., and Halton, J. (1946): "A Milestone in Anæsthesia", *Proc. Roy. Soc. Med.*, **39**, 400.

Griffiths, H. R. (1945): "Curare in Anæsthesia", *J. Amer. med. Ass.*, **127**, 642.

Mushin, W. W., and Wein, R., *et al.* (1949): "Curare-like Actions of Flaxedil", *Lancet*, **i**, 726.

Psychiatry

Bennett, A. E. (1940): "Preventing Traumatic Complications in Convulsive Shock Therapy by Curare", *J. Amer. med. Ass.*, **114**, 322.

Hobson, J. A., and Prescott, F. (1947): "Use of *d*-Tubocurarine Chloride and Thiopentone in E.C.T.", *Brit. med. J.*, **i**, 445.

Tetanus

Belfrage, D. H. (1947): "Tubocurarine in Tetanus", *Lancet*, **ii**, 889.

West, R. (1936): "Intravenous Curarine in the Treatment of Tetanus", *Ibid.*, **i**, 12.

Spastic States

Clarke, C. A., and Hotston, R. D. (1948): "Curare in oil in the Treatment of Spastic Conditions", *Brit. med. J.*, **i**, 289.

Denhoff, E., and Bradley, C. (1942): "Curare Treatment of Spastic Children", *New Engl. J. Med.*, **226**, 411.

Hunter, A. R., and Waterfall, J. M. (1948): "Myanesin in Hyperkinetic States", *Lancet*, **i**, 366.

UNIVERSITY OF MICHIGAN LIBRARIES

REVISION CORNER

TRAVEL SICKNESS

By travel sickness is meant the symptoms of headache, nausea and vomiting which are caused in susceptible persons by the motion of travelling by sea, air, train or automobile. Travel sickness is due to subjection of the body to acceleration in various directions; movement of the body at a steady velocity does not cause travel sickness. For therapeutic purposes it is convenient to consider the sickness caused by sea, air or car travel as identical; but a person may be more susceptible to one form of motion than another, and a remedy successful against one form of motion may be less useful when used against another.

CAUSAL FACTORS

In the past, travel sickness has been thought to originate from various viscera, but it is now generally agreed that it results from disturbances set up in the internal ear. This view receives support from the fact that bilateral labyrinthectomy abolishes motion sickness in dogs which had been previously susceptible (Morton, *et al.*, 1947). A similar interesting observation was made by a clergyman in the middle of the last century. He was bringing a party of eight congenital deaf mutes over the Atlantic in rough weather and noticed that none of them suffered from seasickness. In them labyrinthine activity was presumably absent. Nystagmus is a characteristic feature of the stimulation of the semicircular canals and this sign is never seen in travel sickness. This organ of the internal ear is not therefore thought to be the one responsible for originating the train of symptoms of travel sickness. Modern views implicate the utricular maculæ and their attached otoliths.

PROPHYLAXIS

It is seldom that anything can be done to reduce the motions which cause travel sickness. Nevertheless, the sufferer should endeavour to obtain a front seat in an aeroplane or motor car, and a cabin amidships in a steamer. These are the positions in which the motion of the vehicle is least felt. On board ship the patient should be encouraged to accustom himself to the ship's motion by walking on deck, or to lie on his back. One of the worst positions to adopt is a crouched position over a book. Tyler (1946) found that men ordered to stand in a landing craft were much less likely to suffer sickness than those ordered to crouch in the same craft. Sight, sounds and smells which are liable to cause nausea or vomiting should be avoided. A frequent contributory cause to travel sickness is the alcoholic farewell party of the night before. The sickness which may arise in very susceptible people at merely the sight, sound and smell of a means of transport must be entirely psychogenic; it is therefore doubtful if it will respond to the same measures as true travel sickness.

The importance of psychological factors in true travel sickness is often either over- or under-estimated. It is general naval experience that the overt manifestations of seasickness are less if the sufferer's mind can be diverted. On the other hand, it is my personal experience that seasickness can occur even though one's thoughts are entirely concerned with other matters. Diversion of attention does certainly make the suffering less, and efforts should be made to distract the patient's preoccupation by some light mental or physical activity. It is as unwise

to fuss over a susceptible person as to disregard the physical nature of his complaint and to dismiss the subject as "entirely a matter of nerves and will-power."

DRUG THERAPY

The treatment of travel sickness by drugs is entirely empirical. Judgment of the efficacy of remedies for travel sickness is difficult. At the time of testing there are always at least three variables: (1) the susceptibility of the subjects; (2) the severity of the conditions; (3) the efficacy of the drug. Therefore, for a reliable judgment on any remedy, it is necessary to expose a large number of subjects to the same conditions and to arrange that equal numbers are treated with a placebo or drug of known efficacy as well as the drug under test. It is further desirable that the subjects should be under discipline. Satisfactory conditions may be obtained in a troopship; they are less likely to be obtained in a passenger vessel. The small numbers of subjects that can be carried in aeroplanes or automobiles make these vehicles unsuitable for the testing-out of remedies.

Controlled trials of anti-seasickness remedies were carried out during the last war (Holling, *et al.*, 1944). Ships and men were made specially available for the purpose by military authorities. Of the many remedies reputed to be of value in the treatment of seasickness, only those containing atropine or hyoscine were found to have any detectable beneficial effect. Hyoscine was superior to atropine. Subsequent observations showed that hyoscine is also useful in the prevention of airsickness (Lilienthal, 1945), and the experience of many is that hyoscine is also effective in preventing car-sickness in children. The effective dose of hyoscine, either by mouth or rectally, is 0.6 mg. for an adult. For children between the ages of five and twelve this dose should be halved. The remedy should be taken about half an hour before the causative motion is expected. After the initial dose of 0.6 mg., a dose of 0.3 mg. may be repeated at intervals of six hours for as long as required. In this dosage hyoscine will protect about 60 per cent. of susceptible persons from seasickness. It is somewhat less effective in air- and car-sickness. The drug is more effective if the dose is doubled, but this dosage is likely to cause unpleasant dryness of the mouth.

A further advance in the prevention and treatment of travel sickness occurred when the independent observations of Gay and Carliner (1949) and McEvedy (1949) showed that antihistamine drugs could prevent seasickness. Gay and Carliner were testing the drug "dramamine" (β-diaminoethyl benzohydryl ether 8-chlorotheophyllinate) as a remedy for urticaria and hay fever. They happened to have a patient who was so susceptible to motion sickness that travelling to hospital by trolley car always caused her to vomit. She was given dramamine and found its effect remarkable in curing her car-sickness. Following this lead, well-controlled trials of the drug were carried out on a troopship by Gay and Carliner. Quite independently McEvedy found that the soldiers on board a troopship under treatment with the antihistamine preparation "anthisan" (pyranisamine maleate) were free from seasickness. His subsequent observations showed that this remedy was "at least as acceptable" as hyoscine. The results of Gay and Carliner show that dramamine is superior to hyoscine as an anti-seasickness remedy, preventing sickness in over 90 per cent. of susceptible persons, and proving very effective in curing the condition. It has been found rather less effective in air-sickness (Strickland and Hahn, 1949). Individual reports attest its value in car-sickness. The dosage recommended is 100 mg. by mouth every five hours; if not retained by

mouth it may be given by suppository. "Neoantergan" has also been recommended as valuable in the treatment of travel sickness. The dose is 150 mg. to start with, and the drug is repeated in 100 mg. doses at intervals of eight hours. Children are given a 50 mg. suppository, and thereafter 25 mg. three times a day for as long as necessary. In these doses the drugs should give no unpleasant side-reactions.

Although the prevention of travel sickness is now very effective, it is necessary to consider *the established case* of the condition. The patient should lie down, and theoretically he will obtain most relief if he lies on his back with his eyes open. Until the remedy has been given time to act it is better to give nothing by mouth. In cases in which the remedy cannot be retained when given by mouth it should be given rectally. When the patient is very dehydrated it may be necessary to administer saline per rectum, but recourse to intravenous saline should hardly ever be necessary. Once fluids by mouth can be tolerated, they should be given freely. Water, ginger ale, fruit drinks and champagne are suitable. After the first twelve hours a light diet may be started and gradually increased.

"Dramamine" is an American preparation and is not available in this country. The same drug is sold in Canada as "gravol", and a Swedish firm is also reputed to be producing it. There is no reason to suppose that other antihistamine drugs may not be as, if not more, effective than dramamine. Of the antihistamine preparations available in this country anthisan and neoantergan are known to have some effect. It should be worth while testing the effect of a combination of hyoscine and an antihistamine drug, although in general the prescription of a combination of drugs in travel sickness is not recommended. It is to be hoped that the fighting Services, to whom the subject is important, are investigating the relative value of antihistamine and other drugs as preventatives of seasickness, for they alone have adequate facilities.

H. E. HOLLING, M.B., M.SC., M.R.C.P.
Scientific Staff of the Medical Research Council, Guy's Hospital.

References

Gay, L. N., and Carliner, P. E. (1949): *Science*, **109**, 359.
——,—— (1949): *Bull. Johns Hopk. Hosp.*, **84**, 470.
Holling, H. E., McArdle, B., and Trotter, W. R. (1944): *Lancet*, **i**, 127.
Lilienthal, J. L. (1945): *J. aviat. Med.*, **16**, 59.
McEvedy, M. B. (1949): *Lancet*, **i**, 825.
Morton, G., Cipriani, A., and McEachern, D. (1947): *Arch. Neurol. Psychiat., Chicago*, **57**, 58.
Strickland, B. A., Jun., and Hahn, G. S. (1949): *Science*, **109**, 359.
Tyler, D. B. (1946): *Amer. J. Physiol.*, **146**, 458.

INGROWING TOE NAIL

INGROWING applied to a toe nail is, of course, a misnomer: the nail is not at fault. The two lateral borders of the nail are normally overhung by ordinary skin—the "nail walls"; and it is one of these as it is pushed up and pressed against the side of the nail which causes the trouble. The condition is almost confined to the great toe, is as common in men as in women, and is found with about equal frequency on the medial and lateral sides of the toes; occasionally both sides of the toe are affected simultaneously.

Although it is not clear why one person gets an ingrowing toe nail and another does not, there can be no doubt that lateral pressure by an unsuitable shoe against the toe is an important cause. Another etiological factor is the sharp point of an unwisely trimmed nail.

CLASSIFICATION

It will be of help in discussing treatment if three clinical stages of ingrowing toe nail are described. In the first there is pain along the edge of the nail, increased on walking, and there is slight redness and swelling of the nail wall. The condition is likely to improve rapidly if much walking is avoided and a looser shoe worn; also the sock must not be too tight. Recurrence, however, is liable if pressure on the toe is again permitted. In the second stage there is more swelling of the nail wall so that the skin overhangs the nail to an appreciable extent, and these soft parts by continual pressure against the nail become ulcerated. A discharge, at first serous but later purulent, results. Spontaneous recovery is unlikely to occur at this stage and if left untreated the lesion is likely to pass into the third stage. Here, as the result of continued inflammation, granulation tissue forms and may sprout out profusely; this increases the swelling and causes more pressure against the nail, so that a vicious circle is set up.

TREATMENT

Such a great variety of treatments, some conservative and others operative, have been advised for ingrowing toe nail that it is obvious that none is entirely satisfactory. Many may give good results in many cases, but none in all. Treatment will be discussed under the following headings:—

(1) Prophylaxis
(2) Conservative measures
(3) Operative treatment

Prophylaxis.—Vanity will sometimes prompt people to continue to wear shoes which are uncomfortable. There is no more likely cause of ingrowing toe nail than a shoe which compresses the great toe at each side of the nail: the medial side is compressed directly by the shoe and the lateral indirectly by being pushed against the second toe. A shoe which avoids this must be worn.

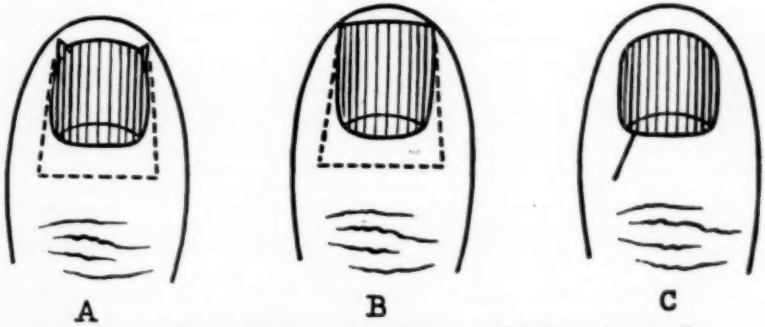


FIG. 1.—(A.) Incorrectly cut nail with spurs. (B.) Correctly cut nail. (C.) Incision for operation.

Correct cutting of the nails is as important in prophylaxis against ingrowing toe nail as is the wearing of suitable shoes. The nail should be so trimmed that the distal corner at each side projects just beyond the end of the nail wall (fig. 1B); in other words, it should be so cut that it may seem a little long at the sides although in the centre it may be cut fairly short so as to be less likely to make a

hole in the sock: this gives a square effect. If the side of the nail is cut short there is a likelihood of a sharp spur being left (fig. 1A), or if not so bad as this, a sharp corner, either of which will be liable to cut into the soft tissues.

Conservative treatment.—In the first stage the condition can often be aborted if the simple precautions of rest and a suitable shoe, as already mentioned, are observed.

In the second stage a fair measure of patience and perseverance will be required to bring about a cure by conservative means. The foot must be used as little as possible and no shoe other than a loose soft slipper allowed. A method which is perhaps worth trying, and which was described in the early part of the 17th century, is the insertion of something between the offending side of the nail and the nail wall. If the side of the nail is gently raised up a little it is possible to put a very thin piece of cotton-wool between it and the soft tissues. Pure glycerin is probably the best substance in which to soak the wool. Sometimes the part is so tender that it is not possible to carry out this little manœuvre.

Another conservative treatment which patients have been known to carry out themselves and which may be helpful, is to cut off a strip of nail one-eighth to a quarter of an inch in width as far back as possible, perhaps even tearing it away at the nail bed.

No conservative treatment is wholly satisfactory and permanently curative, and in an advanced second stage case a decision must be made whether such treatment is worth a trial or whether it is not better to go straight to radical operation as is indicated in the third stage.

Operative treatment.—Surgery is the method of choice in the third stage, and many operations have been devised, although most have the same underlying principle of removing a part or the whole of the nail *including* the nail bed. If only the nail or a part of it is removed a new nail will grow and the trouble with "ingrowing" is likely to arise again. The best operation is that which is simple, causes little pain, heals quickly, requires a very short convalescence, leads to little disfigurement, and gives a cure in a high percentage of cases. The operation which best fulfils these criteria is that of Winograd.

An incision three-eighths of an inch long is made through the thickness of the skin down to the root of the nail, as shown in fig. 1c. Flaps are dissected medially and laterally, exposing at least a third of the nail root. A flat narrow instrument is then passed under the nail from its free edge proximally so that the medial third (or lateral third if that side is affected) is separated from its bed. With sharp-pointed scissors this freed portion of nail is cut away right down to the root. Next the essential step of removing the medial third of the nail root is carried out. The best way is with a small sharp curette, removing every bit; the smallest piece left behind causes trouble. A good deal of force is required and the curetting goes down to the bone. The flaps are then turned back into position but not stitched, and a firm dressing is applied. There is not much pain and the patient walks in a loose shoe after two days. The wound heals quickly.

Some surgeons prefer a formal excision of the nail, nail bed and nail root, combined with removal of the distal half of the distal phalanx; a plantar flap of skin is then sutured back to cover the raw area. This gives good results and is perhaps called for in advanced or recurrent cases: but there is deformity, a good deal of pain, and a much longer convalescence.

JOHN HOSFORD, M.S., F.R.C.S.
Surgeon, St. Bartholomew's Hospital.

NOTES AND QUERIES

Menopausal Dermatitis

QUERY.—A patient, aged about fifty, gets symptoms of the menopause, mostly flushes. These are fairly well controlled, however, by thelœstrol. But at the same time she suffers from intense irritation of her forearms and backs of the hands, worse just before a period. Sometimes a slight erythema (or "blush" as the patient calls it) can be seen, and it is when this appears that the irritation gets really bad; the back of her neck is also affected. I have used antipruritic ointments, and various preparations containing phenol, but so far the condition shows no improvement. I should be most grateful for any suggestion.

REPLY.—A number of dermatoses may be considered as being either directly due to, or influenced by, the menopause (Naegeli and Fellner, 1931; Barber, 1946), but in practice it is often difficult to decide upon the relative importance of diminishing ovarian activity and of nervous tension or fatigue. There are some conditions that are curable by adequate treatment with œstrogen alone, e.g. keratoderma climacterium, the so-called seborrhœic disorders of the menopause, and Civatte's pigmented and reticular poikilodermia, but there are others in which the menopause is but an additional strain to those that so many women have to bear in these days, and œstrogenic therapy is merely an adjunct to the more important measures of rest, sedation, and sympathetic questioning. Naegeli and Fellner (1931) suggest that there is a heightened cutaneous sensibility at the climacteric as there is also at the time of menstruation. It is certainly true that pruritus, with the secondary lichenification from scratching that constitutes neurodermatitis, is one of the most common reactions to stress, and is nowadays much commoner in females than in males.

In the case under discussion your reader remarks that, apart from the itching of her forearms and hands, the "back of the neck" is affected. This presumably is the common neurodermatitis of the nape, a condition almost peculiar to women with which all dermatologists are painfully familiar. It is seen most often at about the time of the climacteric or later, and is in my experience a certain indication of nervous tension from anxiety or fatigue, or at least of a worrying temperament. No doubt the itching elsewhere is of the same nature.

Local applications of antipruritic lotions and creams usually have but a transitory effect upon neurodermatitis, but small doses of X-rays or of thorium-X give more lasting relief. The principles of treatment in a case of this kind are:—

(1) When possible, a complete rest away from home.

(2) A tactful inquiry into the patient's domestic environment and mode of life, and a frank discussion of her difficulties.

(3) Sedation, for example, by small doses of phenobarbitone: ¼ of a grain (16 mg.) after breakfast and lunch and ½ to 1 grain (32 to 65 mg.) at bedtime.

(4) Small doses of an œstrogen, e.g. hexœstrol, 2 mg. daily, taken (since the patient is still menstruating) for a fortnight from the first day of each period, the dose being increased, if necessary, to that required to abolish the flushings completely.

(5) Dietary supplements such as extra milk, vitamin preparations, and, if indicated, iron.

H. W. BARBER, M.B., F.R.C.P.

References

Barber, H. W. (1946): *The Practitioner*, **156**, 333.
Naegeli and Fellner (1931): *Endokrinologie*, **8**, 81.

Hyperhidrosis of the Hands

QUERY.—A female patient of mine, aged twenty-one, and holding a responsible position, complains of severe sweating of her hands. The peculiar thing is that she does not sweat abnormally in any other part of her body. The condition is worse when she becomes heated, and also when excited or nervous. Is there anything I can do to help her, as this sweating appears to be getting worse, and is interfering to a certain extent with her job?

REPLY.—One would like to know much more about this patient—a young woman, with a *responsible* position, complaining of sweating of the hands, which is worse when she is *excited* or *nervous*—the question suggests its own answer. She suffers because of the nervous anxiety called forth by her emotional tensions. We do not know why anxiety in one patient may cause local sweating, in another gastro-intestinal spasms, or in a third tachycardia; but the treatment amounts to much the same in all three. An attempt should be made to get the patient to face the cause, or causes, of the emotional instability in her make-up, to adjust her life and try to minimize the stress which accentuates the anxiety, and to insist on getting enough sleep and proper relaxation. A psychiatrist's help may be needed. The sweating will get worse and interfere with her job probably because the work is not satisfying her, or because she is not up to it, or there is some person whom she meets in her employment who is the disturbing factor. For these or other motives her unconscious may have decided that her present

job is uncongenial, although her reason directs otherwise. Local measures alone are therefore unlikely to succeed, although 5 per cent. formalin dabbed once or twice daily on to the palms may sometimes afford temporary relief. It should be discontinued at the first sign of irritation. X-ray treatment is seldom of value.

C. H. WHITTLE, M.D., F.R.C.P.

Flaking of the Nails

QUERY.—Two of my patients, both women, suffer severely during the winter from flaking of their finger nails; by this I mean that the end of the nails strip back. As a rule this occurs in January and February, but this year it started in November. Is it due to lack of vitamins, or is it a local condition? In neither case is the patient washing more than normal.

REPLY.—The cause of this disorder is unknown. It may be analogous to the chapping of the skin in winter. Treatment is unsatisfactory. There is very little evidence that lack of vitamins plays any part in this disorder. Massive dosage with any or all of the vitamins seldom if ever helps, although they might be tried if other remedies fail. Although these patients are said not to be washing more than normal women, the use of rubber gloves whenever the hands have to go in water is advisable, since it is clear that these nails are more fragile than normal and are probably more liable to damage with alkalis than normal nails. A simple nail cream, such as equal parts of lanoline and petroleum jelly, might also help. If these simple remedies prove ineffective, an iron preparation by mouth might be tried.

H. J. WALLACE, M.D., M.R.C.P.

Pruritus Vulvæ

QUERY.—A female patient, aged twenty-eight, married nine years, with one healthy child aged seven, five years ago developed pruritus vulvæ. The general health is good. Gynæcological examinations have revealed nothing abnormal. A patch of tinea cruris on the thigh three years ago was supposed to be responsible for the condition. This diagnosis has subsequently been confirmed by independent examinations by three dermatologists. The husband is free from tinea infection. Treatment hitherto tried: Castellani's paint; alcoholic gentian violet 2 per cent.; Genatosan cream no. 6; potassium permanganate baths. There has been no relief whatsoever. The vulval mucosa is hypertrophied owing to chronic irritation. There is no leucorrhœic discharge, and menstruation is regular. I shall be grateful for advice on treatment.

REPLY.—From the description and age of the patient the itching may well have been due originally to a ringworm infection, and this is particularly apt to develop into a circumscribed neurodermatitis. This disease is characterized by plaques of lichenification of the labium majus and sometimes hypertrophy of the labium minus. Itching is severe and occurs as bouts, in which the patient has an overmastering desire to tear and rub the affected area. As the name implies, psychological factors are important, and careful inquiries along these lines are strongly indicated, if necessary, by a psychiatrist. In view of the possibility of some traces of the fungus infection still being present, and as it is an excellent anti-pruritic, a preparation of undecylenic acid (e.g. fungicidal ointment (Boots), or decilderm ointment (Duncan Flockhart) oz. 1; K.Y. jelly ad oz. 2), applied night and morning, might well prove helpful. If not, a good response may be obtained from superficial X-ray therapy in a dosage of 750 units once weekly for four or five treatments.

G. A. GRANT PETERKIN, M.B.E., M.B., F.R.C.P.Ed.

Œdema of the Arm following Radical Excision of the Breast

QUERY.—Following a radical operation for carcinoma of the breast in a woman aged forty-three, severe œdema of the arm has developed. Is there any means of treating this (a) by drugs, e.g. mersalyl or other diuretics, or (b) by physiotherapy?

REPLY.—Œdema of the arm following the radical operation for cancer of the breast is due to obstruction of the veins alone or of the veins and lymphatics, and will not therefore be benefited by diuresis. It may be due to the repair of the wound or to extension of the malignant process. Œdema of the arm appearing within a month of the operation means as a rule no more than that the veins are surrounded by repair tissue in the area of the extensive axillary dissection. This early œdema is usually gone by the end of three months. Œdema appearing after six or eight weeks is more likely to be the result of pressure by organizing scar tissue in the line of the incision; it, too, will clear up, but may take a year to do so. This œdema of mechanical origin is distinguished from that due to recurrence, not alone by its early appearance, but by its softness and periodic reduction in size, particularly in the morning. The chief measures that will help recovery are elevation of the arm on pillows when sitting down in the day time and during sleep, and the application of a crêpe bandage from the knuckles to the shoulder during the night. Massage is also useful.

Œdema due to recurrence is seldom seen until six months after the operation, usually later. The œdema is solid, progressive, and is

unaffected by elevation or massage; the cause is the reappearance of malignant tissue somewhere in the course of the veins and lymphatics draining the arm, in the cellular spaces of the axilla, in the glands in the retro-clavicular isthmus, or in those in the posterior triangle of the neck. Treatment is that of inoperable or recurrent cancer. Deep X-ray therapy, if it has not already been given, is probably the most hopeful; disappearance of the induration and relief of the œdema for several years may be obtained, but eventual recurrence is almost inevitable.

Endocrine therapy will often produce a remarkable improvement; treatment with the œstrogens succeeds more often, but if it fails, the androgens may be tried. In either case large doses should be given. Operations for grafting lymphatics or constructing artificial ones are unnecessary in the first group, and worse than useless in the second, since they do no good and merely disseminate cancer cells still more widely. The only operation that can help is the replacement of a tight axillary scar by a pedicled full-thickness graft.

HENEAGE OGILVIE, K.B.E., D.M., M.CH., F.R.C.S.

Otitis Media in Infancy

QUERY.—Could I have authoritative advice on the latest and most efficacious treatment of acute otitis media in infants? My baby eight months ago developed discharging ears after a mild upper respiratory infection, one ear following the other in a matter of a few days with practically no constitutional disturbance. To date the treatment has been dry mopping, spirit drying, and insufflation with boric and iodine powder. After fourteen days the discharge is still present and mucopurulent. (1) What is the place of penicillin or sulphonamides in the treatment of acute ears, either initially, immediately after discharge, and say, after several weeks' discharge? (2) How long can discharging ears be left in infants without surgical interference, and what is the prognosis as regard to hearing? (3) What is the value of antiseptics or antibiotics applied locally? (4) Is surgical drainage advisable in a persistent discharging ear?

REPLY.—(1) The systemic administration of penicillin or sulphonamide is of the greatest value in acute otitis media, before or after discharge. It will often overcome an ear infection, so that pus does not form, and myringotomy is avoided, and it will shorten the severity and duration of acute ear discharge. The effect of administration, after a few weeks of discharge, is less dramatic but still beneficial.

(2) Ear discharge of many weeks' duration may cease, and the drum heal, without subsequent impairment of hearing. Surgical treatment will comprise ensuring adequate drainage of the middle ear, possibly by enlarging a spontaneous perforation which is often inadequate, removing infected adenoids, or washing out an infected nasal accessory sinus. A mastoid operation is only necessary if these measures fail.

(3) None.

(4) Persistent ear discharge may be due to infection having spread to the mastoid cells, and this is, generally speaking, only suspected when the measures outlined in (2) have failed. If the mastoid is infected, drainage is indicated.

Your reader fails to ask one very important question: what is the right local treatment of the discharging ear? The answer is cleanliness, attained either by dry mopping and spirit drops, or by syringing with sterile normal saline, using an all-rubber rat-tailed syringe. The ear must be kept scrupulously clean, and may need attention every four hours. The insufflation of boric and iodine powder is useless, at least in acute discharge in infants and children, and may be harmful in obstructing free discharge of pus. Finally, it is helpful to order ephedrine drops to the nose during acute otitis media, for they will reach the nasopharynx if applied with the child lying on his back, and so help to shrink the swollen and infected adenoids which are often partially responsible for the trouble.

JAMES CROOKS, F.R.C.S.

Recurrent Lumbago

QUERY.—A patient of mine, who is about one stone overweight, has attacks of lumbago. In these attacks there are tender areas of the lumbar muscles which seem to be in spasm. I can cure the attacks by vigorous kneading of these tender spastic areas with methyl salicylate ointment. Unfortunately, however, some contraction of the muscles on the side worse affected is causing some scoliosis, with the cavity of the curve towards the affected side. What is the correct treatment for this please?

REPLY.—From the history of recurrent attacks of backache with muscle spasm it would seem probable that the patient is suffering from recurrent prolapse of a lumbar intervertebral disc. This would cause the muscle to go into spasm and it is possible that there may be some fascial fat nodules which become pressure points when the muscle is in spasm and accentuate the pain. In view of the incipient scoliosis the best line of treatment would be to fit the patient with a lumbo-sacral surgical belt which should prevent further squeezing of the disc. If this is worn consistently for a period of up to a year there is a good chance of the weak points in the annulus fibrosus being able to heal

WILLIAM TEGNER, B.M., M.R.C.P.

PRACTICAL NOTES

Aureomycin in Ophthalmology

A PRELIMINARY report on the use of aureomycin in affections of the eye due to organisms insensitive to penicillin and in eight cases of trachoma is given by Sir Stewart Duke-Elder, D. Ainslie, and A. J. Boase (*British Journal of Ophthalmology*, January 1950, **34**, 30). The cases of mixed infections numbered 33. Aureomycin was given either orally, in the form of aureomycin hydrochloride, 500 to 750 mg. six-hourly up to a total of 20 g., or by instillation of drops, using the following formula:—

Aureomycin hydrochloride	25 mg.
Sodium borate	25 mg.
Sodium chloride	625 mg.
Distilled water	5 ml.

Two drops to be instilled hourly or two-hourly.

For instillation, aureomycin borate must be employed, as the HCl salt is too irritating to the conjunctiva. After mixture with water, aureomycin rapidly loses its antibiotic activity, so that fresh drops must be prepared at least every forty-eight hours. Improvement was noted in blepharitis (1), *H. influenzæ* conjunctivitis (1), keratitis disciformis (1), and marked improvement in a case of inclusion conjunctivitis. Chronic iridocyclitis, dendritic ulcer, punctate keratitis, and herpes ophthalmicus did not respond to treatment. Of the eight cases of trachoma, treated by A. J. Boase of Uganda, all showed marked improvement; in some cases it was dramatic. All were treated by instillation of aureomycin drops. Speaking of this therapeutic trial Sir Stewart Duke-Elder says: "A small quantity of the drug was sent to Uganda, in view of the fact that trachoma of a virulent type is exceedingly common in this country, and the dramatic results reported may be of great importance. To reason from eight cases, of course, is extremely dangerous, and before any conclusion can be reached much larger numbers will require to be treated . . . but if the promise of these early cases is maintained, a therapeutic agent will have been discovered which may bring great changes, socially and economically, to vast tracts of the world".

Oral Diamino-Diphenyl Sulphone in Leprosy

J. LOWE, Director of the Leprosy Research Unit, Nigerian Leprosy Service, Uzakoli, Nigeria, reports the use of diamino-diphenyl sulphone (D.A.D.P.S.) in a series of 88 cases of leprosy (*Lancet*, January 28, 1950, **i**, 145). A regime of oral administration of small doses rising very slowly from 100 mg. daily to a standard of 300 mg. in five weeks was adopted. This regime was found not to produce toxic effects of any consequence and to maintain a blood level of about 1 mg. per 100 ml. In 50 lepromatous cases, including many severe nodular cases, some with respiratory and ophthalmic complications, treated for six to twelve months, there was slow but sure subsidence of the leprous lesions, with shrinkage of nodules and infiltrations and healing of ulcers, and "improvement in the patients' vigour and sense of well-being". In many cases, also, there was diminution in the number of bacilli in the lesions, as shown in "slit smear" preparations. The data of results in this group were: "definite clinical improvement in 36 cases (72 per cent.), definite bacteriological improvement in 31 cases (62 per cent.); and no cases showed clinical or bacteriological deterioration. Febrile reactions (erythema nodosum) occurred in 15 cases (30 per cent.)". The period of treatment (average 9 months) was short, however, and it is stated: "The data so far do not justify a definite claim that D.A.D.P.S. is more rapidly effective than other sulphones in lepromatous cases, though the general impressions of the staff and patients suggest that this is so". In 15 tuberculoid cases, treated for four to ten months, the response was apparent within a month, and sometimes within a fortnight, with complete subsidence of activity of skin lesions within six months. Although the nerve lesions take longer to subside there was already within the short treatment period a beneficial effect on the thickening and inflammation of the nerves, and neuritis was not aggravated by the treatment. In this respect the author writes: "Reconsideration of the sulphone treatment of human tuberculosis may be advisable in the light of the findings recorded here. Preliminary observations show that D.A.D.P.S. treatment as here outlined is well tolerated by patients with tuberculosis of the lungs". The great advantage claimed for D.A.D.P.S. is its lower cost: with D.A.D.P.S. a patient can be treated for one year at the cost of only 14s., whereas with other sulphone drugs the cost of treatment per patient per year is £10 15s. for drugs alone, and such treatment may have to be continued for as long as five years.

Hexæstrol in Chronic Menopausal Rheumatism

NINETEEN patients with chronic non-inflammatory menopausal rheumatism, have been treated at the Medical Policlinic, University of Geneva, with hexœstrol (commercialized under the name of "hormœstrol" [Siegfried] in Switzerland), and the results are recorded by H. Edelstein (*Praxis*, January 19, 1950, **39**,

45). The drug was given orally, in dosage of 5 mg. daily, for two to four weeks, then resumed after an interval of one to two weeks. Of the 19 patients treated, 16 received marked benefit from the treatment: there was diminution or disappearance of pain, and in view of this fact mobility of the joints improved and swelling decreased; there was improvement in the general condition, in some cases, due to better sleep with the cessation of pain and decreased use of analgesics. 31.5 per cent. of the patients showed clinical cure at the end of the treatment period, but required further treatment to conserve the results obtained; 5.3 per cent. were clinically cured after one treatment period of some weeks; 21 per cent. showed clinical cure of one joint, whilst the others remained refractory; in 21 per cent. the pain was greatly improved but had not entirely disappeared; in 5.3 per cent. the effect of the treatment was an improved general condition only, or moderate relief of pain, or improvement in the night pains. Of 3 cases which failed to respond, 2 showed gastric intolerance, and the third had severe lumbo-sacral, sacro-iliac and coxo-femoral affection, shown radiologically. Any leuchorrhœa or menorrhagia resulting from the treatment was always slight and disappeared quickly and spontaneously on cessation of treatment. In conclusion the author states: "We consider that for all chronic, non-inflammatory post-menopausal polyarthropathies synthetic œstrogens in high dosage are the basic treatment of choice".

Skin Diseases in Old Age

"In older patients it is especially necessary that the patient as a whole, and not merely his cutaneous disturbance, be considered and treated". This is the conclusion reached by C. Guy Lane and Ethel M. Rockwood (*New England Journal of Medicine*, November 17, 1949, **241**, 772) as a result of a survey of 2000 patients over sixty years of age with diseases of the skin. Fifty per cent. of the patients suffered from one of five conditions: senile keratosis, epithelioma, seborrhœic keratosis, eczema, or contact dermatitis. Senile keratosis and epithelioma accounted for 28 per cent. of the cases. In discussing treatment, it is pointed out that because of the dryness of the skin in older patients the use of less soap, or of so-called super-fatted soap, is often helpful. In cold weather the use of a thin oil or grease often helps, as does additional protection from the cold. On the other hand, wool may tend to produce irritation. Except in certain well-defined conditions, such as epithelioma, it is often necessary "to compromise with the usual directions given for the care of some skin diseases", e.g. diet. Relief of pruritus is of prime importance. If localized, phenol is still "the best single antipruritic agent". The status of the antihistamine preparations in still *sub judice*. For generalized itching mild sedation is helpful. "In many cases of skin disease improvement or relief was brought about by unusual methods or unacceptable proprietary applications, and it often seemed best to go along with such methods for a while without too sudden changes, with a gradual shift to methods and agents that should really have been better for the patient".

Treatment of Premenstrual Intoxication

THIS name is preferred to "premenstrual tension" by E. J. Stieglitz and S. T. Kimble (*American Journal of the Medical Sciences*, December 1949, **218**, 616) for the condition characterized by emotional irritability, breast engorgement, headache, backache, abdominal fullness and gain of weight, which occurs two to twelve days before the onset of menstruation in many women. Whilst endocrinotherapy may be required in certain cases, the view is advanced that "treatment should be effective, innocuous, simple, inexpensive and free from disturbing side-effects". Details are given of the treatment found to be effective in 91 per cent. of 67 patients, aged sixteen to fifty years. This consisted of ammonium nitrate in enteric-coated capsules: 1 gramme thrice daily for ten days before the onset of menstruation. In addition, treatment was given for the moderately severe anæmia (hæmoglobin under 11 g. per cent.) which was found in 34 (51 per cent.) of the women. It was found essential to institute this treatment before the onset of symptoms; otherwise the results were not so satisfactory. In patients in whom menstruation was irregular, treatment was begun ten days before the expected date of the next period, assuming the shortest cycle for the particular patient, and then continued until menstruation began. The diuresis was found to be enhanced by a liberal fluid intake. Improvement was usually noted during the first course of treatment, but as a rule the optimum response was not obtained until the second or third month of treatment. In those who responded to this treatment, symptoms tended to recur if it was discontinued.

Pantothenic Acid in Muscular Cramps of Pregnancy

A REPORT of the results obtained by the administration of pantothenic acid ("panthénol") in 32 cases of muscular cramps during pregnancy is given by M. Dumont (*Presse Médicale*,

January 7, 1950, **58**, 3). The cases comprised 3 primiparæ, 17 secundiparæ, and 8 multiparæ (4 not specified); in 10 cases varices of the legs were present; in the remaining 22 cases the cramps in the legs were not associated with any venous disturbance. The drug was given by mouth, in dosage of 0.1 g. daily. In 75 per cent. of cases there was total disappearance of the cramps within three to five days of beginning treatment (average); the longest period was ten days. In the 22 patients with no venous complications, results were excellent in 19 and good in 3 (86 per cent. cure rate). The author draws attention to the fact that in some cases muscular cramps in pregnant women disappear spontaneously: in 2 cases in the series the intensity of the cramps had decreased before the institution of treatment; nevertheless, of the cases treated, 18 had had violent cramps nightly, and in 4 cases day and night. He concludes with the statement: ". . . panthénol should take an important place in the vitamin therapy of pregnancy . . ."

Methionine in Napkin Dermatitis

A REPORT of the results obtained by the use of methionine in the treatment of over 500 infants with napkin dermatitis due to ammoniacal urine is given by L. S. Goldstein (*Archives of Pediatrics*, December 1949, **66**, 553). Methionine granulated ("metiogran"—10 per cent. dl-methionine plus 90 per cent. dextrose and lactose) was employed, 1 teaspoonful for infants under one year, and 1½ to 2 teaspoonsful for those of one to two years, daily. The preparation is stated to be soluble and to mix readily in the daily milk formula. Success was obtained in all cases except three; the ammonia disappeared from the urine in three to four days, and the napkin dermatitis and ulcerations cleared up in seven to ten days. The only local treatment used in conjunction was the application of zinc ointment. Treatment was continued for at least one week, and with the appearance of cyclic recurrences granulated methionine was prescribed for another week or two. In the three cases that failed to respond, in one case the infant refused the formula because of flavour, in the second the infant vomited, and in the third a generalized macular dermatitis developed. All three cases responded well when 60 grains (4 g.) of thiamine daily were substituted for 1 teaspoonful (3 grains = 0.2 g.) of methionine granulated. In conclusion it is stated: "There are multiple causes for ammoniacal urine and napkin dermatitis in infants. Allergy appears to be an important etiological factor. Methionine and thiamine effectively inhibit the formation of excess metabolic ammonia and its appearance in the urine".

Treatment of Subacute Combined Degeneration of the Cord

IN a series of 44 patients with subacute combined degeneration of the cord, observed over periods ranging from six months to six years, C. C. Ungley (*Brain*, September 1949, **72**, 382) found no statistical significance between the effects of crude and refined liver extracts. Significant improvement was obtained in 41 cases, and this was maintained in all except three patients in whom relapse followed an intercurrent illness. It is stressed that "it is not enough to base requirements [of liver] on the amounts needed to maintain normal red blood cell levels or to prevent sore tongue. Dosage must be based on the amounts needed to improve or arrest the nervous lesions". The weekly dosage of liver extract required is that hæmopoietically equivalent to about 40 microgrammes of B_{12}. After six months this can usually be reduced by one-half, provided it is increased again on any evidence of relapse or if intercurrent infection occurs. Details are also given of eight patients treated with B_{12} for periods ranging from nine to nineteen months, from which it is concluded that vitamin B_{12} is "as effective as liver extract not only in pernicious anæmia but in subacute combined degeneration . . . Except perhaps for patients who have become sensitized to some impurity in liver fractions, the pure substance has no advantage over commercial liver extracts, particularly if their potency is determined clinically and microbiologically in terms of vitamin B_{12}". The recommended dosage of B_{12} is 40 microgrammes weekly for the first six months, and then half this amount as maintenance dosage. "At the least sign of relapse, or if intercurrent infection supervenes, dosage should be increased until complete arrest of the neurological condition is assured".

Tetanus and Curare

CURARE in oil ("tubarine": Burroughs Wellcome) has been used in the case of a ten-year old boy with tetanus, for symptomatic treatment in conjunction with antitoxin therapy, by F. Hauser (*Schweizerische Medizinische Wochenschrift*, December 31, 1949, **79**, 1273). The drug was given by subcutaneous injection of 0.3 ml. daily, later increased to 0.5 ml. There was marked decrease in rigors and hyperreflexia, and the subjective action of the drug was most satisfactory: the use of narcotics was avoided, and thereby the general condition, the circulation and nutrition were favourably influenced. On the basis of results the author "sees a great advance in the treatment of tetanus with tubarine".

REVIEWS OF BOOKS

Applied Medicine. By G. E. Beaumont, D.M., F.R.C.P., D.P.H. London: J. & A. Churchill Ltd., 1950. Pp. ix and 140. Figures 74, some in colour. Price 30*s.*

The vivid accounts that Hippocrates left of the patients to whom he was called in consultation can still be read. There is a quality in the portrayal of an illness as seen in an individual patient that is lacking from the necessarily more general description of the textbooks. Dr. Beaumont has revived a method of instruction in the natural history of disease of which examples have lately become so few. To turn the pages of Trousseau, or even the popular medical journals of Victorian days, is to discover clinical descriptions of a quality rare to-day. The first half of Dr. Beaumont's book is given to a selection of case histories descriptive of a number of arbitrarily chosen diseases. They make good reading. The latter part of the book is chiefly devoted to a series of "cases demonstrated at the bedside" in which an almost ideal physician questions an almost ideal student. The case is presented by question and answer in the Socratic method and, although this tends to make tedious reading at times, has the advantage of presenting with clarity a logical development of the argument. The book concludes with a few pages of discerning aphorisms. The student will find in this book a pleasant change from the more stereotyped style of a textbook of medicine, and he could not fail to remember much that is so palatably and descriptively presented. If only the binding had been equal to the beautifully produced letterpress, this book would be handsome indeed.

Stillbirths: their Epidemiology and Social Significance. By Ian Sutherland, D.Phil., F.S.S. London: Oxford University Press, 1949. Pp. xii and 95. Figures 4. Price 7*s.* 6*d.*

In just under one hundred pages Dr. Sutherland has condensed a thorough and interesting statistical survey of the stillbirth rate in England, Scotland and Wales since this condition first became notifiable. Geographical variations within the British Isles and comparable figures for certain other European countries are given, and the relative importance of medical, biological and social factors is carefully analysed. Dr. Sutherland's book was written before the publication last year of the Report on Neonatal Mortality and Morbidity by a joint Committee of the Royal College of Obstetricians and Gynæcologists and the British Pædiatric Association, and they cover closely related subjects and form valuable companion reports. In spite of its statistical approach, the book is very readable and should be of great value to obstetricians, public health authorities and those interested in nutritional problems.

Diagnosis and Therapy of Gynæcological Endocrine Disorders. By C. L. Buxton, M.D., and E. T. Engle, Ph.D. Springfield, Illinois: Charles C Thomas; Oxford: Blackwell Scientific Publications Ltd., 1949. Pp. viii and 62. Price 14*s.* 6*d.*

This small, compact, easily read monograph of some sixty pages was written especially for the practitioner, who will find it of absorbing interest. The physiology and hormonal control of menstruation and the various sex hormones which are of value clinically are described; their source, method of administration and efficacy are outlined. The investigation, diagnosis and treatment of the common gynæcological endocrine disorders are discussed in a clear, concise and practical manner. This book can be recommended with confidence as it summarizes well-established facts; it makes no extravagant claims and indicates briefly when to use the sex hormones, why they are used and how to use them. The practitioner will find the lines of treatment advocated invaluable in his everyday work.

The Vitamins in Medical Practice. By J. Shafar, M.D., M.R.C.P., D.P.H. London: Staples Press Ltd., 1949. Pp. 383. Price 25*s.*

Any practitioner going abroad where vitamin deficiencies are common should certainly take this book with him. Anyone who wants to know what results he may expect from vitamin therapy in a large variety of clinical disorders will find this a useful key to the literature. The author has achieved something that is long overdue, a synopsis on the vitamins as they concern the practitioner, culled from 1,685 well-selected and cited references. Many practitioners must by now be bewildered by enthusiastic reports of the value of vitamins in many conditions in which their own results have been disappointing. This book sanely weighs the sober against the sensational in the literature on vitamin therapy. Although perhaps too long and too learned for the busy practitioner with few nutritional problems, it could be read with advantage by those working for higher examinations, and possibly also by their examiners.

Occupational Eye Diseases and Injuries. By JOSEPH MINTON, F.R.C.S. London: William Heinemann (Medical Books) Ltd., 1949. Pp. viii and 184. Figures 24. Price 21*s.*

THERE has been a lack of a book dealing with this subject. The present work deals not only with actual diseases and injuries, however, but adds to its usefulness by reviewing visual requirements in various occupations and the possibility of employing the patient after an injury. One feature that becomes prominent is the mental attitude of the patient, a subject that could with advantage be given a full chapter of its own in any future edition. The book will be particularly useful in reminding the medical man that his responsibility cannot be considered as discharged with the clinical treatment of an affected organ.

Human Personality and its Minor Disorders. By WILLIAM HARROWES, M.D., M.R.C.P.ED., D.P.M., F.R.S.E. Edinburgh: E. & S. Livingstone Ltd., 1949. Pp. vii and 260. Price 15*s.*

THIS book restates the concepts of Adolf Meyer which are used in dealing with human personality, normal and abnormal. This could not be done better than by Dr. Harrowes, who has been a student and close personal friend of the great American psychiatrist from whose school emanated such movements as mental hygiene, child guidance, and the training of psychiatric social workers. The author describes questions designed to elicit information on how the individual, in view of his inborn constitution, has reacted to environmental stress and has from early childhood acquired his own particular patterns of conduct. The virtue of this approach is that it avoids dogma, keeps close to common sense, and provides room for any supplementary investigations in this vast field, thus anchoring psychiatry to general medicine and to the scientific method. Little is said within the scope of this essay, however, concerning the actual art of curing the patient, the author relying chiefly on easing the patient's burden and on self-understanding. Nevertheless, there is nothing in the Meyerian system to contraindicate those therapeutic techniques (e.g. narco-analysis, hypnosis, modified insulin therapy, aversion treatment of alcohol) which hasten recovery and improve prognosis.

NEW EDITIONS

MANY improvements have been incorporated in *Modern Professional Nursing*, edited by Mildred Hainsworth, in its second edition (Caxton Publishing Co., Ltd., 90*s.*, 4 vols.). The chapters on health and hygiene have been brought up to date, and also those on materia medica, therapeutics and dietetics. In Medical Nursing the section on peptic ulcer is broader and far more in keeping with modern views than in many textbooks of medicine. It is questionable whether nurses require the wealth of detail given in the bacteriological tables; yet, despite their increasing importance, viruses are dismissed all too briefly. The production of the new edition is good, and general editor, contributors and publishers may justly feel that they have produced a most useful textbook of nursing.

The Common Diseases of the Skin, by R. Cranston Low, M.D., F.R.C.P.ED., F.R.S.E., and G. A. Grant Peterkin, M.B.E., M.B., F.R.C.P.ED., in its fourth edition (Oliver and Boyd, 21*s.*) appears in a new format although the general structure of previous editions has been retained. Advances in treatment and some new illustrations have been included. The work, which is based on lectures given by the late Dr. Cranston Low, is compiled as a handbook for students and medical practitioners, and the practical advice on diagnosis and treatment, and some useful formulæ, should commend it to the latter.

A NUMBER of new sections have been added to *A Textbook of Surgery*, by American Authors, edited by Frederick Christopher, B.S., M.D., F.A.C.S., in its fifth edition (W. B. Saunders Company, 65*s.*), including those on tumours of the brain and intracranial abscesses; tumours of the tendons and tendon sheaths; surgical diseases of the pancreas; surgery of the spleen; chronic prostatitis; pyogenic infections of the skin; chemotherapy of surgical infections; and management of the surgical diabetic patient. These are a few features chosen at random from the new edition, which is well produced and generously illustrated.

Das Menschliche Knochenmark, by Karl Rohr, in its second edition (George Thieme, Stuttgart, DM 47.50) is really a new book for English readers, since few copies of the first edition, published in 1940, reached this country. It is a textbook about every aspect of bone marrow and therefore contains a good deal about general hæmatology, and gives a balanced idea of present-day Continental hæmatology. The work is well illustrated, mainly by monochrome photographs of smears and histological sections, and 24 colour reproductions from paintings are included.

The contents of the April issue, which will contain a symposium on "Athletic Injuries", will be found on page lxxviii.

Notes and Preparations, see page lxv.
Fifty Years Ago, see page lxxi.